PHYSICAL ACTIVITY IN ADULTS WITH KNEE OSTEOARTHRITIS

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ABSTRACT

PHYSICAL ACTIVITY IN ADULTS WITH KNEE OSTEOARTHRITIS

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Purpose: This dissertation has two primary aims; 1) to better understand how various physical, psychological, and general health factors influence physical activity (PA) and 2) to better understand different clinical phenotypes in people with knee osteoarthritis (OA) and functional outcomes, including PA.

Methods: This dissertation utilizes data from the 48-month follow up of the Osteoarthritis Initiative, an observational longitudinal study of 4,796 participants examining onset and progression of knee OA in community dwelling adults between the age of 45-79. For the first study: 403 participants in a subset of participants using accelerometer- derived PA data, were analyzed for significant correlates of total PA time to estimate total PA using a linear regression model with bootstrapped standard errors. The second study includes data from 1,057 participants to perform a K-Mean Cluster analysis using body mass index, depressive symptoms, strength and radiographic evidence. One Way Analysis of Variance analysis and a Tukey's post-hoc test was utilized to compare clinical outcomes between clusters including PA, function and pain.

Results: In our first study: Over three-quarters of our sample did not meet the recommended volumes of PA. Negative associations were noted between higher BMI and total PA, comorbid conditions and total PA, and increasing age and total PA. A positive

association was noted between diverting attention as a coping strategy and higher volumes of PA.

In our second study: The cluster analysis identified 5 clinical phenotypes. Significant differences were noted between phenotypic groups in all clinical outcomes measured.

Conclusion: Older adults with knee OA are not meeting recommendations for total PA, which can improve function and attenuate the effects of functional decline and disability. Four major factors were associated with total PA levels in a population with mild to moderate knee OA: co-morbidities, age, BMI, and the diverting attention coping strategy. In our second study, we identified five phenotypes of individuals with knee osteoarthritis and revealed differential clinical outcomes based on phenotypes. Understanding clinical differences between phenotypes may enable us to efficiently and effectively target our interventions to optimize PA and functional outcomes in people with knee osteoarthritis.

DEDICATION

I am honored to dedicate this dissertation to my parents, who have pushed me to be the best possible version of myself, and always believing in my success. It is because of their confidence and encouragement that I have pushed to complete this degree. I also dedicate this dissertation to my husband, who has stood by my side through this process with nothing but positivity, strength and love.

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L.A.B.

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Chapter I

INTRODUCTION

In older adults, arthritis ranks as one of the most common causes of disability and affects over 14 million adults in the United States.[1,2] The prevalence of individuals diagnosed with arthritis is expected to increase to 71.5 million, or 25% of the population by 2030.[1] In one year alone, direct medical costs attributed to osteoarthritis totaled 81 billion dollars, along with 43 billion dollars in lost earnings due to disability and time away from work.[3] Osteoarthritis has also been linked to metabolic and systemic conditions such as hypertension, hypercholesterolemia and high blood glucose levels, which can lead to larger health implications and further increase the economic burden.[4-6] Our population is aging and the proportion of older adults with osteoarthritis is increasing. Given the significant health and economic burden of this disease, it becomes increasingly more important that we better understand not only the disease process but also those factors and strategies that can be used to modulate progression of this chronic condition.[7]

Osteoarthritis, a multifactorial disease, manifests itself in a variety of clinical presentations. Two people may have the same diagnosis and radiographic classification; however, their physical exam and subjective complaints of pain, functional limitations and disability may vary significantly, making treatment both challenging and unique to each patient.[8,9] We cannot simply look at a radiograph and assume a certain level of pain

and dysfunction. Many factors, both physical and psychological, have been associated with the expression of pain and dysfunction in this population.

Recently, researchers have begun utilizing phenotypes aimed at understanding different clinical presentations in patients with osteoarthritis.[9] Recognizing these different clinical clusters, or phenotypes are important to discover patterns that may lead to an expansion of treatment options beyond the management of musculoskeletal dysfunction. As a result, there are many different methods to treatment that can provide individualized care for each patient who presents with such a variable disease.

What we do know is physical activity is critical for general health and can lead to a reduction in cardiovascular risk factors, but it can also assists in decreasing pain and stiffness, maintaining muscle strength, preventing functional decline and improving quality of life.[10] [11] Physical activity guidelines for adults are comprised of at least 150 minutes of moderate and/or 75 minutes of vigorous physical activity per week, as recommended by The American College of Sports Medicine. [12] We also know that adults with mobility limitations, such as osteoarthritis, who engage in greater levels of physical activity have greater muscle strength, perform better in functional tasks and have better health outcomes than those with lower levels of physical activity.[13] [14] Regular physical activity has been a consistent recommendation for individuals with knee osteoarthritis.[15] however, individuals with osteoarthritis are consistently less physically active compared to their healthy counterparts.[16,17,18]

Many factors, including general health, psychological, and physical factors influence physical activity behaviors. This dissertation has two primary aims; 1) to better understand how various physical, psychological, and general health factors influence

physical activity and 2) to better understand different clinical phenotypes in people with knee osteoarthritis and their associated functional outcomes, including physical activity. Overall, insights gained from these two studies have the potential to impact the conservative approach to treatment for a large segment of the American population with osteoarthritis.

Dissertation Format

This dissertation is broken up into two distinct research studies in people with knee osteoarthritis. The purpose of the first study is to determine which self-reported psychological, functional and health related outcomes including coping strategies are associated with total physical activity time, as measured by accelerometry, in people with knee osteoarthritis.

The purpose of the second paper is to identify clinical phenotypes in a sample of people with knee osteoarthritis and to examine and compare clinical outcomes including physical activity, functional mobility, pain, coping strategies and comorbidities between these phenotypes. The two research questions: 1) Do distinct clinical phenotypes exist in this study population, and if so, what are they? and 2) How do clinical outcomes, including physical activity, physical function, health status, pain and coping strategies, differ across the clinical phenotypes identified in this study population?

We hypothesized that this study population would present with the same classification of clinical phenotypes as described in the literature.[19,20] We looked at

between group differences for physical activity, function, health status, coping strategies and pain measures across the various clinical phenotypes identified in this study population. We hypothesized people in the Strong Muscle Strength and Minimal Joint Disease Phenotypes would have the highest volume of physical activity and functional mobility, as well as the lowest pain and least use of passive coping strategies than other phenotypes. Further, we hypothesized those within the Depressive Symptoms and Weak Phenotypes would have significantly lower physical activity and function and higher levels of pain. Finally, we hypothesized that the Depressive Symptoms Phenotype would have the highest catastrophizing score compared to the other Phenotypes.

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Chapter II

CORRELATES OF PHYSICAL ACTIVITY IN PEOPLE WITH KNEE OSTEOARTHRITIS

Abstract

Purpose: To identify psychological, functional and health-related outcomes associated with physical activity in people with knee osteoarthritis (OA).

Methods: We analyzed 403 participants with knee OA from the Osteoarthritis Initiative who also had complete accelerometer- derived physical activity (PA) data with frequent knee symptoms in the past month or for at least one month during the past 12 months, described as "pain, aching or stiffness in or around the knee on most days" and radiographic tibiofemoral knee OA on the fixed flexion radiograph with a Kellgren and Lawrence (KL) grade ≥2. Significant correlates (sociodemographic, psychological, functional and health related measures) of total physical activity time were used to estimate total PA using a linear regression model with bootstrapped standard errors.

Results: Over three-quarters of our sample did not meet the recommended volumes of PA. Negative associations were noted between higher BMI and total PA, comorbid conditions and total PA, and increasing age and total PA. A positive association was noted between diverting attention as a coping strategy and higher volumes of PA. No significant relationship was noted between pain and total PA.

Conclusion: Older adults with knee OA are not meeting recommendations for total PA, which can improve function and attenuate the effects of functional decline and disability. Four major factors were associated with total physical activity levels in a population with mild to moderate knee OA: co-morbidities, age, BMI, and the diverting attention coping strategy.

Introduction

Knee osteoarthritis is estimated to affect over 14 million adults in the United States.[1] Obesity, joint trauma, repetitive movements , advancing age, and genetics are risk factors associated with the development of osteoarthritis [2-4], which is a multifactorial disease of unknown pathogenesis that is manifested by a variety of presentations. Even given the same diagnosis and radiographic classification of knee osteoarthritis, individuals may present very differently in terms of pain, functional limitations and disability.[5,6] Older adults with knee osteoarthritis often experience pain, functional limitations and physical inactivity, which are leading contributory factors in functional decline.[7]

The American College of Sports Medicine recommends all adults participate in at least 150 minutes of moderate and/or 75 minutes of vigorous physical activity per week.[8] As compared to adults without osteoarthritis, people with osteoarthritis more often are insufficiently physically active and less likely to meet these recommended targets of physical activity.[9,10] Furthermore, individuals with the lowest volumes of physical activity have a greater prevalence of co-morbid chronic diseases.[11]

Regular physical activity is essential for individuals with knee osteoarthritis, not only for reduction of risks for chronic diseases and overall health benefits, but also for pain and stiffness reduction, maintenance of muscle strength, prevention of functional decline, and improved quality of life.[12,13] Individuals with mobility limitations who engage in greater volumes of physical activity have better health outcomes, compared with those who participate in more sedentary behaviors.[14]

For older adults with chronic conditions such as osteoarthritis that may limit participation in physical activity, the ACSM recommends physical activity to tolerance, even at volumes less than the recommended targets for physical activity.[8] Modest increases in physical activity in insufficiently active individuals with osteoarthritis or risk factors for developing osteoarthritis can reduce disability.[15] Recent studies using data from the National Health and Nutrition Examination Survey (NHANES) report that physical activity, even at light intensity, is associated with better cardiovascular health and decreased mortality risk.[16] The Physical Activity Guidelines Advisory Committee also recently suggested that any amount of PA is beneficial, even at light intensity.[17] PA of all intensities can result in health benefits and can be recommended for individuals with OA who are unable or unwilling to engage in greater amounts of PA.

Many factors such as physical, psychological, and general health factors may influence physical activity behavior in people with osteoarthritis. Understanding how these factors influence movement may enable effective promotions to assist individuals to become more physically active. Psychological factors, such as how people cope with pain and osteoarthritis as a disease process, may play a role in physical activity behaviors.[18]

Coping strategies are defined based on their perceived outcomes, or the individual's understanding of how much control they have over a situation. People with knee osteoarthritis who practice more active or adaptive coping strategies have less disability and better physical function, compared to individuals who engage in more passive, or maladaptive coping strategies.[20] In a study examining discrepancies between radiographic evidence and functional limitations in osteoarthritis, people with higher radiographic evidence of osteoarthritis who use active coping strategies such as positive self-statements had higher functional mobility compared with those using passive strategies.[21] Research is lacking in discovering associations between coping strategies and physical activity behaviors.

Therefore, the purpose of this paper is to identify psychological, functional and health-related outcomes associated with physical activity volume in people with osteoarthritis.

Methods

Participants and Procedures

This study was a secondary analysis of participants in the Osteoarthritis Initiative (OAI), a publicly and privately funded longitudinal multicenter observational study examining the onset and progression of knee osteoarthritis (ClinicalTrials.gov #NCT00080171). The OAI consists of 4,796 community dwelling men and women between the ages of 45 and 79 years of all ethnic backgrounds who had knee osteoarthritis at the time of enrollment (2004-2006). The participants were recruited from

four clinical sites around the United States (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH). No treatments were performed as part of the OAI; however, participants were asked to report any treatment they were receiving as part of their medical care during the data collection clinical visits. Details of the OAI study protocol and inclusion and exclusion criteria can be publicly viewed at http://www.oai.epi-ucsf.org.[22]

The analytical sample in the current study included a group of OAI participants who met the diagnostic criteria for definite osteoarthritis, and who also had complete accelerometer derived physical activity data at the 48-month collection period (2008-2010). Participants were categorized as having definite osteoarthritis if they met two criteria: 1) frequent knee symptoms in the past month or for at least one month during the past 12 months, described as "pain, aching or stiffness in or around the knee on most days" and; 2) radiographic tibiofemoral knee OA on the fixed flexion radiograph with a Kellgren and Lawrence (K-L) grade ≥2.[23] Participants were excluded from the current study sample if they did not have definite OA or presented with rheumatoid arthritis, inflammatory arthritis, psoriatic arthritis or ankylosing spondylitis defined by self-report at the 48 month follow up period. Participants were also excluded if they did not wear the ActiGraph GT1M uniaxial accelerometer (ActiGraph; Pensacola, FL) for at least 4 days for a minimum of 10 hours per day.[24,25] Based on these inclusion and exclusion criteria, 431 participants were eligible for this study. (Figure 1)

Measures

Sociodemographics

Sociodemographic information was included to describe the participants including age, sex, race, education level and BMI.

Physical Activity

Physical activity was measured using ActiGraph GT1M uniaxial accelerometers (ActiGraph; Pensacola, FL). Scripted instructions were delivered to each participant during enrollment. Participants were asked to wear the accelerometer at the natural waist on the right hip in line with the axilla for seven consecutive days during all waking hours, except when engaged in water activities. ActiGraphs were then returned to the OAI for data analysis. Freedson cut points were used to categorize the intensity of physical activity (i.e., light and moderate to vigorous intensity physical activity).[26] Total physical activity time was used for this analysis, which combined the time in light and moderate to vigorous intensity physical activity.

Coping Data: Coping Strategies Questionnaire (CSQ)

The Coping Strategies Questionnaire is a criterion- and construct-validated instrument for community-living individuals with knee osteoarthritis that measures coping strategies for managing OA.[27] This questionnaire consists of 14 questions assessing 7 distinct coping strategies in people with OA: Diverting Attention,

Reinterpreting Pain Sensations, Catastrophizing, Ignoring Sensations, Praying and Hoping, Coping Self Statements, and Increased Behavioral Activities. Participants rated how often they used each coping strategy on a scale from 0-7, where 0= never, 3=sometimes and 7= always.[28]

WOMAC Pain Score

The Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC) is a measure of three different domains including pain, stiffness and disability during daily tasks through a 24-item questionnaire. A higher score in each subscale represents increased pain, stiffness, or disability. For this analysis, we examined the WOMAC pain subscore, which is a highly valid and reliable scale in a population with knee osteoarthritis and has been utilized in a variety of clinical trials.[29-31] The WOMAC pain subscore has a possible score 0-20. The OAI investigators collected data on both left and right knees independent of each other. Consistent with prior studies, the current study analyzed the single knee with the highest WOMAC score representing the most limiting knee for the individual.[32,33]

Health-Related Quality of Life

The Medical Outcomes Study Questionnaire Short Form-12 (SF-12) is a questionnaire that assesses self-reported health status, functioning, and well-being .[34,35] This is a shorter form of the SF-36, and it has been validated in people with knee osteoarthritis.[34] The SF-12 covers 8 domains of health-related quality of life including

physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional and mental health. The first four measures are summarized into the physical health composite score, and the sum of the last four from the mental health composite score. Composite scores are standardized so that 50 is the mean for the general population of the US (and 10 is the standard deviation); therefore scores greater than 50 are indicative of better mental and physical health-related quality of life as compared to the population mean.[36]

Falls (Last 12 months)

Falls were assessed using a single question asking, "Have you fallen in the past 12 months?", with a dichotomous answer choice (yes or no).

Charlson Co-morbidity Index

The Charlson comorbidity index was used to classify each person's risk of disability, morbidity, and mortality based on their comorbid conditions.[37] Nineteen diseases are included, and weighted according to their associations with mortality; higher scores are associated with increased risk of mortality.[37,38]

Medications

Participants were asked to bring in or record all prescription medications they took in the past 30 days. The total number of medications taken per day was recorded.

Statistical Analysis

The data were analyzed in MATLAB[39] and *R*.[40] Of the 431eligible participants, complete data sets were identified for 359 participants. A test of the missing data mechanism was conducted using the "MissMech" package [41], and data were found to be missing completely at random ($p > 0.05$)[42]. After conducting multiple imputations in *R*, a total of 403 cases were rendered complete for further analyses in MATLAB.

Tests for linear trends between total time spent in PA and self-reported psychological, functional, and health related outcomes were initially conducted using a series of Pearson's correlations. Significant correlates of total PA time were then simultaneously used to estimate TPA using a linear regression model; data were found to meet all assumptions of the test. Given that not all correlates were significant explanatory covariates, a more parsimonious model for estimating TPA was specified using a lasso regression. Covariates from the lasso model that were not constrained to equal 0 were then extracted as the final subset of variables in the model including age, graduate school graduate, falls, BMI, comorbidity, CSQ ignoring pain sensations, CSQ diverting attention, CSQ Catastrophizing and medication number. Finally, a linear regression model was run with bootstrapped standard errors (with replacement; $n = 1000$ iterations) using only the lasso-defined subset of variables in order to facilitate covariate interpretation in the more parsimonious model. The significance level for all analyses was set *a priori* at $\alpha<0.05$.

Results

Demographics

More than half of the final sample was female, with ages for the entire sample ranging from 49 to 83 years. Over 80% of the participants were overweight or obese, having a BMI $\geq$ 30 m•kg^2. Most participants had mild to moderate radiographic evidence of osteoarthritis as described on the Kellgren and Lawrence (KL) scale, and the remaining participants had a KL score showing end-stage osteoarthritis. The participants were highly educated, with most having at least some college education. Most of the participants were White, and less than 20% identified as a minority, most frequently identified as Black. Respondents reported on average experiencing only mild pain on the WOMAC scale. (Table 1)

Physical Activity

On average, participants wore the accelerometers for 14.8 ± 1.5 hours per day over 6.7 ± 0.74 days. Over this mean wear time, participants engaged in an average of 4.9 ±1.4 hours of total PA time per day. They participated in about half of the recommended 150 minutes of moderate to vigorous PA per week. Only 18% of the participants met the recommended targets for moderate to vigorous physical activity of ≥30 minutes of moderate or vigorous physical activity per day. Light PA was the primary PA engaged in by the participants, engaging in 4.6 ± 1.3 hours of light PA per day.

Results from the in the initial linear regression model showed that, age, BMI and diverting attention on the CSQ were significant correlates of total PA (Table 2). The lasso model with the lowest cross-validated mean squared error (RMS; 0.00629), revealed graduate school education, falls, age, BMI, comorbidities, medication number and self-statements, diverting attention, catastrophizing on the CSQ as significant correlates of total PA, while all other covariates were constrained to equal zero. (Table 3) The final bootstrapped linear regression model with the subset of lasso-derived covariates, showed that on average, when all other covariates are held constant, a one-year increase in age was associated with a 3.2 minute decrease in TPA per day, a one unit increase in the Charlson Comorbidity Scale was associated with a 9.9 minute decrease in TPA per day, and a one unit increase in BMI was associated with a 1.6 minute decrease in TPA per day. We also found a significant positive association between diverting attention on the CSQ; with a 1 unit increase on the CSQ diverting attention subscale, there was an increase of 8.55 minute per day in TPA (Table 4). The final adjusted R^2 value for this model is 0.22.

Discussion

Most of the older adults in our study did not meet recommended guidelines for total physical activity. In this study, we identified self-reported psychological, functional and health related correlates of total physical activity time in people with knee osteoarthritis. The presence of comorbidities, increased age, and high BMI were associated with lower total physical activity in people with knee OA; whereas the use of

diverting attention as a coping strategy was associated with higher levels of total physical activity participation.

Comorbidities

The physiologic consequence of one chronic condition can influence or exacerbate another, and adversely affect overall health.[43] For example, the NHANES study showed an association between symptomatic knee osteoarthritis and long-term disability, particularly involving ambulation and transfers.[16] Difficulties with these tasks are also associated with increased risk for heart disease, pulmonary disease, and hypertension.[43] Comorbid conditions can influence depression, fatigue, poor function and worsening symptoms of knee OA.[44] Our study showed a negative association between comorbid conditions and total physical activity time in people with knee OA, which is consistent with a study of veterans with hip and knee OA measured by questionnaires, suggesting intervening in this population can help mitigate the impact of these comorbidities on physical activity and function.[44]

Age

With increasing age, adults participate in significantly less moderate to vigorous physical activity and also spend more time in sedentary behaviors.[24,45] Consistent with the literature, our study also reports that increasing age is negatively associated with total physical activity in people with knee OA.[46] This is important due to the fact that physical

activity has been shown to improve physical function and potentially attenuate the effects of functional decline and disability as adults age.[25,47,48]

BMI

Our study also confirms previous findings that older adults with mobility limitations, such as osteoarthritis, engage in less physical activity and have higher BMIs compared to their healthy counterparts.[14] We found a negative association between total physical activity time and OAI participants with higher BMIs. This poses a problem in this particular population because increased body weight itself increases the risk of development and progression of knee osteoarthritis and disability, and, when combined with insufficient PA, these individuals are likely poised for more rapid decline toward functional limitations and disability. [49-52]

Diverting Attention

To manage disability and pain, people with OA may use a variety of coping strategies, both active and passive strategies; active strategies being more effective in managing pain than passive strategies.[53,54,55] The only coping strategy associated with engagement in higher volumes of physical activity in our study sample was diverting attention. We were unable to find any studies investigating any potential association between diverting attention and physical activity, however, prior studies examining how people with chronic pain cope with pain describe diverting attention as an active and positively adaptive coping strategy.[55,56]

Disease Progression and Pain

As noted earlier, knee OA is multifactorial disease with a wide range of presentations. While pain is often associated with decreased physical activity [57], our study found no significant relationship between these two variables. However, our population, included persons with Kellgren and Lawrence scores between 2 and 3, mild to moderate osteoarthritis (83.55%) who reported low levels of pain, with an average WOMAC pain score of 4.7/20. Chmelo et al[44] and Farr et al[45] found similar results in accelerometer-based study samples of people with mildly painful OA[44,45] and mild to moderate KL scores. This may suggest that pain is not be a key driver of physical inactivity in people with this level of disease. Results may be different in persons with end stage knee OA, as defined by a KL score of 4. Liu et al used Osteoarthritis Initiative data to study persons with end stage knee OA who spent greater time in both light and moderate to vigorous physical activity over a one-year period. They found that this level of activity associated with greater symptoms of OA including pain, stiffness and function.[58]

Similar questions can be raised about the coping strategies used. Our study showed a positive correlation between the diverting attention coping strategy and increased total physical activity time. However, effective coping strategies may change as pain severity levels or chronicity changes.[56,59] Future longitudinal studies are needed to investigate the impact various coping strategies, such as diverting attention may have on total physical activity time and the role of diverting attention in physical activity prescription.

Future Directions and Potential Clinical Applications

About 50% of healthy adults do not meet national guidelines for daily physical activity and this number becomes more pronounced in older adults and in particular in older adults with chronic conditions, such as knee OA.[60] Over three-quarters of our sample did not meet the recommended volumes of daily physical activity. Although these targets are recommended for all adults, in adults with chronic conditions presenting with barriers to physical activity, such as OA, participation in physical activity to tolerance can be beneficial, even at light intensities.[8,17] Even when guidelines are not met, increasing the volume of moderate to vigorous physical activity is associated with reduced disability, and all cause morbidity and mortality rates. [15,61,62] Loprinzi et al suggest that if older adults with mobility limitations increased the amount of time they participated in light physical activity, their rate ratio of chronic diseases would decrease.[14] To combat the sequelae of chronic disease, it is important for the health care community to focus on getting this population much more physically active earlier.[17]

As the 2018 Physical Activity Guidelines Advisory Committee suggested, preventing chronic disease and maintaining functional independence has significant public health implications.[17] In our study, we identified 4 major factors associated with total physical activity levels in a population with mild to moderate knee OA: co-morbidities, age, BMI, and the diverting attention coping strategy. While age is not a modifiable factor, the other three factors can be modified. Future studies should focus on: 1) identifying effective strategies to impact physical activity in this population; 2)

identify different phenotypes of people related to physical activity behavior to be able to better target interventions; and 3) longitudinal studies examining strategies to maintain physical activity and function through the disease progression.

A strength to this paper is the large sample size of community dwelling older adults with knee osteoarthritis utilizing accelerometers, which provides objectively measured data for analysis. This paper is a cross-sectional analysis which limits the ability to assess causation. This paper also includes a highly educated, primarily white sample, that may not allow for generalizability to the general population, which would encourage future work in a more diverse population. Understanding the depth and breadth of osteoarthritis must also take into chronicity of time, prior surgical procedures, strength, anxiety, and concomitant injuries of other joints that limit mobility, and a wide array of confounding variables, which were not addressed in this paper.

Conclusion

OA is a complex multifactorial health condition that is progressive in nature and often presents with multiple co-morbid conditions, as well as decreases in physical activity, significant health-related decline and functional deterioration. Age, BMI and comorbidities are associated with lower total physical activity time. Diverting attention, as a psychological coping strategy, is associated with increased total physical activity time in people with mild to moderate osteoarthritis. Incorporating and encouraging individuals to participate in any level of physical activity may have significant public health implications including reducing long term disability, mortality, and morbidity;

however more research is warranted to more fully understand these relationships across the lifecycle of individuals with OA.

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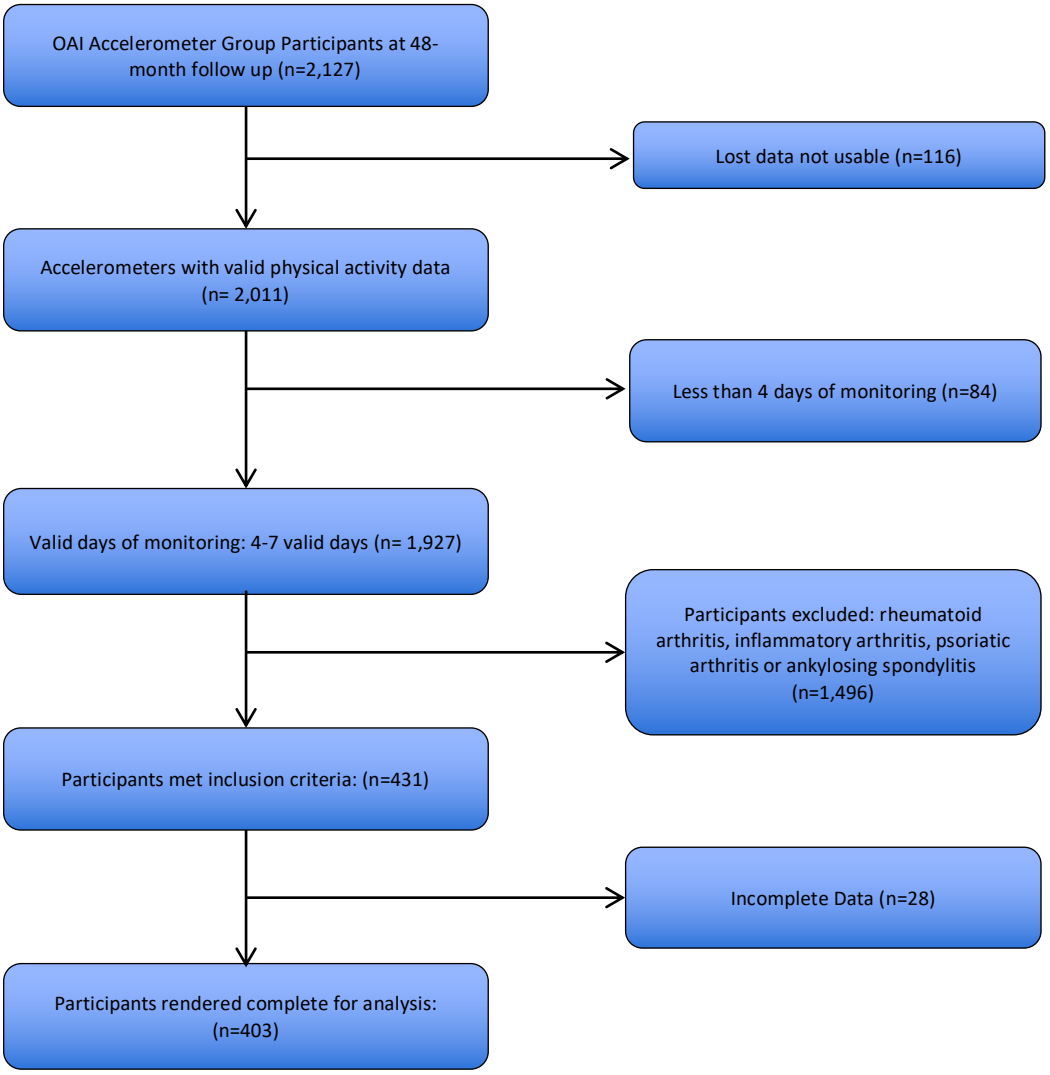

Figure 1.
Study participant flow

Table 1.
Characteristics of 193 Men and 238 Women Participants in the OAI Initiative

Characteristics	Mean (SD) or percent
Age (years)	65.2 (8.7)
BMI Category (%)	
<24.9 m/kg2	18.6
25-29.9 m/kg2	34.0
>30 m/kg2	47.5
Sex (%)	
Male	44.8
Female	55.2
Education Level (%)	
Some College	34.2
College Grad/ Some Graduate School	31.2
Graduate School Graduate	34.9
Race (%)	
White	82.1
Black	16.7
Asian	0.5
Other	0.7
Falls in the past year (5)	
No	63.9
Yes	36.1
Kellgren and Lawrence Score (KL) (%)	
KL Grade 2	45.5
KL Grade 3	38.1
KL Grade 4	16.5
WOMAC Pain Score (%)	4.8 (3.6)
0-5	65.7
6-10	26.6
11-15	6.9
16-20	0.7
Medication (number)	3.9 (2.5)
Physical Activity Time (min/wk)	
Light	278.7 (79.0)
Moderate to Vigorous	16.4 (17.6)
Total Physical Activity	295.0 (86.3)
Charlson Comorbidity Scale Score	0.6 (1.0)

CSQ Score	
Ignoring Pain Sensations	3.2(1.6)
Self Statements	3.6 (1.9)
Praying and Hoping	1.0 (1.5)
Reinterpreting Pain Sensations	0.9 (1.2)
Diverting Attention	1.3 (1.7)
Increased Behavior	2.7 (1.8)
Catastrophizing	0.7 (1.1)
SF-12 Scores	
Mental Health Composite	54.5 (8.6)
Physical Health Composite	45.8 (8.9)

Table 2.
Associations between PA and sociodemographic, health and physiological variables

	Estimates	SE	T statistic	p-Value
Intercept	301.39	13.041	23.111	<0.001
Sex (Female)	5.7127	8.5134	0.67103	0.50261
Education				
Some College	-16.405	14.617	-1.1223	0.26243
College Some Grad	-9.985	13.506	-0.73928	0.46019
Grad	-21.85	13.662	-1.5993	0.11057
Fall (Yes)	12.116	8.3305	1.4544	0.14664
Age	-3.5503	0.49763	-7.1345	<0.001
BMI	-1.171	0.85737	-2.0027	0.045912
Charlson Comorbidity Scale	-7.9353	4.2183	-1.8812	0.060709
CSQ Ignoring Pain Sensations	3.1751	2.6762	1.1864	0.23619
CSQ Self Statements	-1.4315	2.6451	-0.54117	0.5887
CSQ Praying and Hoping	-0.21946	3.5529	-0.06177	0.95078
CSQ Reinterpreting Pain Sensations	-3.6165	3.6	-1.0046	0.31573
CSQ Diverting Attention	8.7885	3.3602	2.6155	0.0092628
CSQ Increased Behavior	1.1649	2.9591	0.39368	0.69404
CSQ Catastrophizing	-2.8057	4.0951	-0.68513	0.49368
Medication Number	-3.6147	1.8568	-1.9467	0.052296
SF-12 Mental Health Composite	0.2849	0.49872	0.57127	0.56815
SF-12 Physical Health Composite	0.09911	0.56838	0.17437	0.86167
WOMAC Pain Subscore	0.43136	1.3259	0.32533	0.74511

Results from Linear regression model. Bolded variables **P= <0.05**

Table 3: Lasso Model. Association between physical activity and the most significant sociodemographic, health and physiological variables

	Estimated Betas
Sex Female	0
Education	
Some College	0
College and Grad	0
Grad	-5.5781
Falls (yes)	4.5925
Age	-3.1164
BMI	-1.1798
Comorbidity	-7.2101
CSQ Ignoring Pain Sensations	0.29837
CSQ Self Statements	0
CSQ Praying and Hoping	0
CSQ Reinterpreting Pain Sensations	0
CSQ Diverting Attention	5.978
CSQ Increasing Behavior	0
CSQ Catastrophizing	-0.29028
Medication Number	-2.6681
SF 12 Mental	0
SF 12 Physical	0
Select WOMAC Pain	0

Bolded variables **P= <0.05**

Table 4.

Bootstrapped Linear Regression Model for Total Physical Activity Time Using the Significant Variables from the Lasso Model

	ß	SE	t	P-value
Intercept	296.32	5.74	51.60	<0.001
Education (Grad)	-13.61	7.97	-1.70	>0.05
Falls (yes)	11.35	8.27	1.37	>0.05
Age	-3.27	0.53	-6.21	<0.001
BMI	-1.67	0.81	-2.06	<0.05
Charlson Comorbidity Scale	-9.89	3.94	-2.51	<0.05
CSQ Ignoring Pain Sensations	1.97	2.40	0.82	>0.05
CSQ Diverting Attention	8.55	2.57	3.32	<0.001
CSQ Catastrophizing	-3.61	3.57	-1.01	>0.05
Medication Number	-0.13	0.09	-1.48	>0.05

Bolded variables **P= <0.05**

Chapter III

USING CLINICAL PHENOTYPES TO UNDERSTAND PHYSICAL ACTIVITY IN PEOPLE WITH KNEE OSTEOARTHRITIS

Abstract

Purpose: The purpose of this paper was to 1) identify phenotypes of people with knee osteoarthrosis (OA) and, 2) compare common clinical outcomes, including physical activity, functional mobility, pain, coping strategies and comorbidities, between the clinical phenotypes identified.

Methods: Data from 1,057 participants from the Osteoarthritis Initiative (OAI) were used for this analysis. A K-Mean Cluster analysis was performed using body mass index, depressive symptoms, strength and radiographic evidence. One Way Analysis of Variance analysis with a Tukey's post-hoc test was used to compare clinical outcomes between clusters including physical activity, function and pain.

Results: The cluster analysis identified 5 clinical phenotypes: Strong Muscle Strength, Minimal Joint Disease, Obese and Weak, Non-Obese and Weak and Depressive Symptoms. Significant differences were noted between phenotypes in all clinical outcomes measured. Individuals in the High Muscle Strength and Minimal Joint Disease Phenotypes had the highest volume of physical activity and functional mobility, as well as the lowest pain and least use of passive coping strategies than other phenotypes. Those

within the Depressive Symptoms and Obese and Weak Phenotypes had significantly lower physical activity and function and higher levels of pain. The Depressive Symptoms Phenotype had the highest catastrophizing score compared to all other phenotypes. ***Conclusions:*** This study identified five phenotypes of individuals with knee osteoarthritis and revealed differential clinical outcomes based on phenotypes. Understanding clinical differences between phenotypes may enable us to efficiently and effectively target our interventions to optimize physical activity and functional outcomes in people with knee osteoarthritis.

Introduction

Knee osteoarthritis is multifactorial in nature, impacting millions of older adults. Because of the wide variability in the presentation of knee osteoarthritis, recent research has begun to identify various clinical subtypes or phenotypes of people based on combinations of different characteristics.[1] Phenotypes can be defined as a compilation of similar traits into groups that interact with each other in small variations; but differ between other groups in larger variations, creating distinct categories.[2] The intent of identifying these categories or subtypes is to enable clinicians to create more precise treatment strategies targeted to specific presentations of knee OA.[3]

Very few studies have been published to identify these clinical phenotypes in individuals with knee osteoarthritis. Knoop et al. identified clinical phenotypes in people with knee osteoarthritis from the Osteoarthritis Initiative based on the following characteristics body mass index (BMI), mean isometric muscle strength; radiographic

knee osteoarthritis, measured by the Kellgren and Lawrence Scale (KL), and depression, measured by the Centers for Epidemiologic Study Depression Scale (CES-D).[2,3] They chose these characteristics because they are commonly assessed in a clinical setting, and have strong associations with disease presentation, progression, and outcomes. These researchers identified five clinical phenotypes of individuals with knee osteoarthritis: "Minimal Joint Disease," "Strong Muscle Strength," "Non- Obese and Weak," "Obese and Weak," and "Depressive Symptoms." Van Der Esch et al. used a different database, the Amsterdam Osteoarthritis Cohort, to validate these phenotypes.[3] While they looked at some common clinical outcomes and reported significant differences between phenotypes, their outcomes were limited to pain and function. Neither study reported on differences in physical activity behavior which has been associated with significantly less disability lower rates of disease progression and improved function.[4,5] They also did not address coping strategies, health status and objectively measured function which previous work by this author found were associated with physical activity.

Physical activity has been reported to be effective in reducing painful symptoms and stiffness, maintaining or improving muscle strength, enhancing overall quality of life, and preventing functional decline in individuals with knee OA,.[6,7] When compared to age and gender matched peers, individuals with knee OA are less likely to achieve recommended targets for daily physical activity.[8,9] Pain, functional limitations and physical inactivity are all factors that can accelerate functional decline in older adults with knee osteoarthritis.[10] Greater volumes of regular participation in physical activity are associated with improved health outcomes in people with mobility limitations.[11] Given that phenotypes are uniquely different, it is important to understand how physical activity

might differ across phenotypes, as it may influence exercise prescription. Currently, there is no evidence that looks at physical activity across phenotypes.

In the first paper of this dissertation, we aimed to understand how various clinical factors including physical, psychological, and general health factors might impact physical activity, a common treatment recommendation in this population. What we discovered was that increased age, BMI and comorbidities were associated with lower total physical activity time, while diverting attention, as a psychological coping strategy, was associated with higher physical activity time in people with mild to moderate knee OA. However, considerable variability was not explained by the model, potentially because of the presence of different clinical phenotypes. Identifying phenotypes may provide more targeted information in relationship to clinical outcomes, including physical activity, function, pain, psychological, and general health factors, in this population.

Given the limited evidence currently available on clinical phenotypes in individuals with knee OA, our first purpose was to identify the clinical phenotypes present in a broader sample of people from the Osteoarthritis Initiative and compare them to those presented in the literature.[2,3] Once these phenotypes were identified in our study sample, the second purpose was to build upon the outcomes of the first study in this dissertation, by examining and comparing clinical outcomes including physical activity, functional mobility, pain, coping strategies and comorbidities between phenotypes. The two research questions are: 1) Do distinct clinical phenotypes exist in this study population, and if so, what are they? and 2) How do clinical outcomes, including physical activity, physical function, health status, pain and coping strategies, differ across the clinical phenotypes identified in this study population?

We hypothesize that the clinical phenotypes or clusters identified in this study population will be consistent with the clinical phenotypes found in the literature.[2,3] We will examine between phenotypic group differences for physical activity, function, health status, coping strategies and pain measures across the various clinical phenotypes identified in this study population. We hypothesize people in the Strong Muscle Strength and Minimal Joint Disease Phenotypes would have the highest volume of physical activity and functional mobility, as well as the lowest pain and least use of passive coping strategies than other phenotypes. Further, we hypothesize those within the Depressive Symptoms and Weak Phenotypes would have significantly lower physical activity and function, and higher levels of pain. Finally, we hypothesize that the Depressive Symptoms Phenotype would have the highest catastrophizing score compared to the other Phenotypes.

Methods

Participants and procedures

This study sample was drawn from participants from the Osteoarthritis Initiative (OAI), which is a longitudinal multicenter observational study examining 4,796 community dwelling men and women 45-79 years of age who are at risk for or have knee osteoarthritis (ClinicalTrials.gov #NCT00080171). Study protocols, inclusion and exclusion criteria, and details of the OAI can be publicly viewed at http://www.oai.epi-ucsf.org.[12] The current study included participants from the OAI at the 48-month

collection period (2008-2010). Participants were included if they reported frequent knee symptoms in the past month or for at least one month during the past 12 months, described as "pain, aching or stiffness in or around the knee on most days". Participants were excluded if they had incomplete data, self-reported rheumatoid arthritis, inflammatory arthritis, psoriatic arthritis, or ankylosing spondylitis. There were no exclusions based on radiographic evidence of OA which resulted in data from 1066 participants eligible for this study.[13]

Measures

Clustering Variables

Clustering variables are the specific variables used to determine phenotypes in the K-Means cluster analysis. The variables used in this analysis include: body mass index, radiographic evidence of OA, quadriceps strength, and depression. *Body Mass Index* was measured using height in meters and weight in kilograms and obesity was defined as a BMI of greater than 30 kg/m^2.[14] *Radiographic Evidence of OA* was defined by the Kellgren-Lawrence Score (KL) on a fixed flexion knee radiograph. The KL score ranges from 0-4 and definite radiographic evidence of osteoarthritis is defined as a score of 2 or greater on this scale.[15] The limb with the knee with the highest KL score, or greatest evidence of radiographic OA, was used for this study as it best represents overall burden to the participant.[16] *Quadriceps Strength* was the mean score of the maximal left and right isometric quadriceps strength, measured in newtons.[17] *Depression* was measured

using the score on the Center for Epidemiologic Studies Depression Scale (CES-D), which is a 20-question scale with total score from 0-60. A score of 16 or greater suggests depressive symptoms.[18]

Clinical Measures

Physical activity was measured using the Physical Activity for the Elderly Scale (PASE). The survey queries about participation in leisure, occupational and household physical activities and assesses the intensity and duration of PA over one-week.[19] Construct validity on the PASE scale has been identified using correlations between peak oxygen uptake, resting heart rate, blood pressure and percentage body fat. [20] The total time to complete a 400-meter walk test was used to measure *Physical function*. This 400 meter walk test has been used extensively to assess strength, power and mobility limitations in older adults.[21,22] *Pain* was measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscore, which is a commonly used measure validated for use in people with knee osteoarthritis.[23,24] The OAI investigators collected WOMAC pain data in both left and right knees independent of each other. Consistent with prior studies, the current study analyzed the mean score between left and right knees, representing the total burden of limitation for an individual.[3] *Health status* was measured by the Charlson Comorbidity Index, which classifies each person's risk of disability, morbidity, and mortality according to the presence of select comorbid conditions.[25] Two sub-scales of the Coping Strategies Questionnaire, diverting attention and catastrophizing, were used as measured of two different *methods of coping*,

the first, classified as an active strategy and the second, as a passive, or maladaptive strategy.[26,27]

Statistical Analysis

Statistical analyses were conducted using IBM SPSS (Version 25). Descriptive statistics were determined using means and standard deviations for continuous variable and percentage for categorical variables.

To address the first purpose of this study, a K-means cluster analysis was conducted to identify distinct phenotypes in this study population of people with knee OA.[2] Cluster analysis categorized observations into groups of individuals who appeared similar to each other across multiple variables. The goal of a cluster analysis is to partition the observations into smaller groups, or clusters, where participants only belong in one group resulting in low variance within clusters and high variance between clusters, resulting in the phenotypes described in this paper.[28] The four variables used in the cluster analysis were BMI, KL, quadriceps strength, and CES-D. Because the units of measurement for these variables were different, prior to analyses, the variables were standardized using the z-score. Boxplots were created and the extreme outliers were eliminated from the sample using the interquartile range rule of 3 in SPSS.[29] After the scores were standardized, 9 outliers were discovered and removed from the data set, resulting in 1057 participants. The variables were entered into the K-Mean Cluster in order of highest to lowest correlation with physical activity using a Spearman's Rho Analysis: quadricep strength, CESD, KL and BMI. The cluster analysis was iterated until

the data converged, which was achieved when there was no change in cluster centers. The maximum absolute coordinate change for any center of 0.000 was statistically used to indicate convergence was achieved. This required 24 iterations.

To address the second purpose of this study, once the cluster analysis was complete, a one-way Analysis of Variance (ANOVA) was used to compare clinical outcomes across the phenotypic groups. A post hoc Tukey Honestly Significant Difference (HSD) Test was used when there were significant main effects to compare between groups.

Results

Demographic characteristics of the study population are described in Table 5. Participants in our sample ranged from 49-83 years old with a mean age of 64.5 ± 8.83 years, and 58.6% of the population were female. Participants were primarily Caucasian (84.4%), with a small portion identifying as Black/African American, Hispanic or Other (13.3%, 0.5%, 1.8%, respectively). The participants were well educated, and 61% of the sample having a college degree or higher. 18.8% of our population had a KL of 0, with no definite radiographic finding of knee osteoarthritis and 37.4% of our sample had moderate to severe knee osteoarthritis (KL of 3- 4).[15]

The means, in the standardized z-score, of the cluster centers are depicted in Figure 2 and the characteristics of each cluster are described in Table 6. The clusters were named based on the most defining symptom.

Clinical Measures

There were significant between group differences in all groups as measured by the One-Way Analysis of Variance. Significant findings were based on a P-value less than or equal to 0.05. The post hoc comparisons are reported in Table 7, and Figure 3 shows the mean scores for the selected clinical outcomes across the phenotypes.

The PASE score was significantly higher in the Strong Muscle Strength and Minimal Joint Disease Phenotypes compared to all other groups. The PASE score was significantly higher in the Minimal Joint Disease Phenotype as compared to the Depressive Symptoms Phenotype. There were no significant differences between the PASE Score for the Strong Muscle Strength and Minimal Joint Disease Phenotype; or between the Non-Obese and Weak and Obese and Weak Phenotypes.

Similarly, the 400-meter walk test times were significantly faster in the Minimal Joint Disease and Strong Muscle Strength Phenotypes as compared to the other phenotypes. No significant differences in the mean walk test scores were noted among the other 3 phenotypes.

Comorbidity scores were significantly higher in the Obese and Weak and Depressive Symptoms Phenotypes compared to all other phenotypes, however, there were no significant differences between the Obese and Weak and Depressive Symptoms Phenotypes.

The WOMAC Pain score was significantly higher in the Depressive Symptoms Phenotype compared to all other phenotypes. The Obese and Weak Phenotype also had significantly higher pain scores than the Minimal Joint Disease and Strong Muscle

Strength Phenotype. Lastly, the Non-Obese and Weak Phenotype had significantly higher mean scores compared to the Minimal Joint Disease Phenotype.

The Depressive Symptoms Phenotype had the highest CSQ Catastrophizing score compared to all other phenotypes. The Depressive Symptoms, Obese and Weak and Non-Obese and Weak Phenotypes had a significantly higher score on the CSQ Diverting Attention Scale compared to the Strong Muscle Strength Group.

Discussion

The results of this study confirm the existence of 5 clinical phenotypes in individuals with knee osteoarthritis and these phenotypes are consistent with those previously reported in the literature. After identifying the phenotypes, we examined clinical outcomes across these phenotypes and found significant between group differences for all clinical outcomes measured, which again confirmed our initial hypotheses.

Physical Activity

Physical activity is critical to decreasing symptoms, preventing decline, and improving quality of life in people with knee osteoarthritis. [6,7] Higher scores on the PASE Scale have been associated with better function over time in older adults with knee osteoarthritis, consistent with the Strong Muscle Strength and Minimal Joint Disease Phenotypes.[30]

The Weak Phenotypes had lower physical activity scores compared to the Strong Muscle Strength and Minimal Joint Disease Phenotypes, suggesting that quadriceps strength may be associated with increased physical activity. Increasing quadriceps strength has been associated with decreasing pain and increasing functional outcomes in people with knee osteoarthritis.[31]

Although not significantly different than the Non-Obese and Weak group, the Obese and Weak Phenotype had lower level of physical activity, which is consistent with literature suggesting that obesity is also associated with insufficient physical activity.[32] Obesity increases the risk of development and progression of knee osteoarthritis, alters gait mechanics and speed leading to limitations in ambulation and can increase the progression of disability associated with knee osteoarthritis. [33-39]

The lowest reported physical activity scores and the lowest functional outcomes of all phenotypes was noted in our Depressive Symptoms Phenotype. This may be the result of multiple compounding factors, including psychological distress consisting of fear, anxiety, catastrophizing, depressive symptoms and altered pain cognitions surrounding chronic pain.[40]

Functional Mobility

Slower 400 meter walk times have been associated with higher rates of mortality, cardiovascular disease, mobility limitations and disability.[41] In addition to lower levels of physical activity, participants in the Obese and Weak, Non-Obese and Weak, and Depressive Symptoms phenotypes also had the slowest 400-meter walk test times, indicating poorer physical function. Although there may be many reasons for decreased

physical activity and function, one of the more powerful predictors of future functional limitations is the avoidance of physical activities.[42] Although avoiding activity may have the desired short-term effect of decreasing pain for some, in the long term, this can lead to inactivity, poor function, decreased fitness and loss of muscular strength; a cycle that leads to ultimate decline.[8,43] The concomitant decrease in fitness and strength can worsen symptoms of osteoarthritis, reinforcing a cycle of increased pain, physical inactivity, and greater functional limitations. [27,43]

Health Status

As Pisters et al., noted, multiple comorbidities are predictors of functional limitations.[42] In our sample, the Obese and Weak and Depressive Symptoms Phenotypes had significantly higher scores in the Charlson Comorbidity Scale as compared to the Strong Muscle Strength Phenotype. Interestingly, the phenotype with the highest age, the Non-Obese and Weak Phenotype had the second lowest Charlson Comorbidity score. This may suggest that obesity and depressive symptoms have a greater association with multimorbidity, defined as two or more chronic health conditions.[44] In obese adults, the risk of having multiple comorbid conditions, particularly cardiometabolic, is significantly higher compared to normal weight adults.[45] Also, people with multiple comorbid conditions are also twice as likely to have depression compared to those without.[46]

Pain

Pain is another factor that must considered in individuals with knee osteoarthritis. In our sample, significantly higher levels of pain were noted in both Weak Phenotypes than in the Strong Muscle Strength and Minimal Joint Disease Phenotypes. Literature indicates quadriceps weakness has been significantly associated with pain and disability in people with knee osteoarthritis, which may be partially explained by reflex inhibition, in which increased pain shuts down the function of the quadriceps muscle.[47,48]

The Depressive Symptoms Phenotype had the highest reported levels of pain, which is particularly interesting because only a small percentage of individuals in this group had moderate to severe radiographic knee osteoarthritis. Along with altered pain cognitions, prior studies have documented the influence of central sensitization, which has been more commonly reported in people with greater pain catastrophizing, depression, and anxiety.[49] Central sensitization is a maladaptive change to the sensory processing system, causing hyperalgesia and widespread decreases in pain and pressure thresholds throughout their entire system, not just in a specific joint or region, which can influence the perception of more widespread and significant pain.[50,49,51]

Coping Strategies

Finally, coping strategies have been reported to influence pain perception, depression, functional limitations, and physical inactivity. Catastrophizing has been defined as a passive coping strategy with a magnified emotional focus on pain sensations and feeling helpless in the face of pain.[52] In our sample, catastrophizing was used more

by individuals with the Depressive Symptoms Phenotype, which is consistent both with the literature and our hypothesis. People with long standing chronic pain more consistently report using passive coping strategies, which have a greater impact on functional limitation and pain compared to active strategies.[53] Pain catastrophizing has been associated with a higher level of pain, depression, disability, physical activity and slower walking speeds.[52,54,55]

Diverting attention, is classified as an active coping strategy, that enables the individual to shift attention to a more pleasant experience.[53] In the first study of this dissertation, diverting attention was associated with increased physical activity and improved function in people with knee osteoarthritis. This was not evident in this study where the phenotypes with greatest use of the diverting attention strategy had poorer clinical outcomes. It is possible that phenotypic clusters more specifically identified the subset of individuals using the diverting attention strategy. While looking at this group as a whole, diverting attention may seem to be a positive strategy, when associated specific to a cluster, it may be different. This is not, however, inconsistent with literature in people with chronic low back pain. For example, Rosenstiel and Keefe reported a similar association between diverting attention and high levels of pain and functional limitations, suggesting it may be helpful to cope with pain in the short term, however it may not be effective as a long term strategy.[56] Interestingly, participants in our study who use diverting attention at higher levels displayed a similar profile that matched chronic low back pain, such as higher comorbid conditions and more psychological distress.[57]

Recommendations

Identifying distinct phenotypes of people with knee osteoarthritis may help better target interventions to enhance functional outcomes and optimize physical activity. Although individuals in the Strong Muscle Strength and Minimal Joint Disease Phenotypes reported the highest level of PA, this population remains consistently less active compared to their age-matched peers.[9] Focusing on gradually increasing levels of PA may help minimize development of co-morbidities such as obesity or cardiovascular disease, improve overall function, and decrease disability, even if the intensity of physical activity does not meet guidelines.[58] Quadriceps strengthening should be incorporated in all long term management programs for knee osteoarthritis, particularly in people in both Weak Phenotypes. Individuals with obesity, particularly those in the Obese and Weak phenotype, may be better served using a different approach that incorporates not only graduated increases of daily physical activity but also more a comprehensive program that includes nutritional counseling, diet, strength training and medical screening for management of comorbid conditions.[59-61]

Finally, numerous studies report the influence of depressive symptoms and psychological distress on functional outcomes in people with knee osteoarthritis. People in the Depressive Phenotype of our study showed the lowest level of PA, slowest walk time, higher number of co-morbidities and highest level of pain. Given these findings, we would suggest that those with marked depressive symptoms would likely benefit most by focusing first on the management of underlying depressive symptoms.[62] Encouragement of physical activity should also be incorporated in the long term management of people in

this phenotype due to the influence of physical activity in reducing depressive symptoms.[63] Lastly, encouraging active coping strategies is an important component of osteoarthritis self-management programs, which along with exercise, are strongly recommended in the conservative approach to managing knee osteoarthritis by the American Academy of Orthopedic Surgeons.[64]

This was a retrospective study using an existing patient data base examining a cross section of older adults with knee osteoarthritis. We identified distinct phenotypes and examined various clinical outcomes; however, given the multifactorial nature of this disease, it is possible that other factors not included in this study could have impacted the convergence of these clusters (e.g., length of disease, bilateral involvement, concomitant musculoskeletal disorders, current treatment).

Future Studies

Our study included individuals reporting frequent knee pain in at least one month over the previous 12 months; 18.8% had knee pain but no radiographic evidence of knee osteoarthritis. Future studies on the discordance between pain and radiographic evidence of knee osteoarthritis may lead to a refinement of the phenotypes identified and may impact future treatment strategies. Furthermore, we sought to identify the clinical clustering variables used in previous studies (i.e. BMI, strength, depression and KL score); however future studies using clinical variables such as genetics, anxiety, self-efficacy, laxity or chondral changes noted on MRI may again further refine the phenotypes present in this disease entity. Cluster analysis may be used in a variety of

disease entities to identify more homogeneous sub-types, enabling clinicians to develop more targeted approaches to intervention.

Conclusion

Knee osteoarthritis impacts a broad range of individuals who present with different symptoms, each potentially requiring a different approach to care. In our study, individuals with knee osteoarthritis clustered into 5 distinct phenotypes: Strong Muscle Strength, Minimal Joint Disease, Non-Obese and Weak, Obese and Weak and Depressive Symptoms. Between group differences were noted in clinical measures including physical activity, physical function, pain, health status and coping strategies. The highest levels of physical activity and function were noted in the Strong Muscle Strength and Minimal Joint Disease Phenotypes; while the lowest scores for all outcome measures were reported in the Depressive Symptoms Phenotype. Although certain risk factors for developing osteoarthritis are not modifiable, others lifestyle factors, such as weight management, physical activity, muscle strengthening exercises and addressing depressive symptoms can play a significant role in modifying the risk, progression and symptoms of knee osteoarthritis.

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Table 5.

Characteristics of the Osteoarthritis Initiative Study Sample (N= 1066)

Clinical Characteristics	**% or mean ± SD**
Age (years)	64.5 ± 8.8
Sex, %	
Male	41.4
Female	58.6
Race, %	
White	84.3
African American	13.4
Asian	0.5
Other Non-White	1.8
Education, %	
Less Than HS Graduate	2.0
HS Graduate	11.2
Some College	24.9
College Graduate	21.8
Some Graduate School	7.9
Graduate Degree	32.1
Radiographic Knee OA, %	
KL Score 0	18.8
KL Score 1	13.1
KL Score 2	30.8
KL Score 3	25
KL Score 4	12.4
Quadriceps Strength (N)	225.4 ± 91.3
BMI (kg/m^2)	29.5 ± 4.9
Obese, %	45.6
CES-D Score	7.2 ± 7.5
>16 %	12.6
PASE Score	157.3 ± 81.4
400 Meter Walk Time (s)	314.1 ± 57.8
WOMAC Pain Score	3.3 ± 2.7
CSQ Diverting Attention Score	1.12± 1.6
CSQ Catastrophizing Score	0.7 ± 1.2

Table values are mean ± standard deviations or %. Abbreviations: KL= Kellgren and Lawrence Score BMI= Body Mass Index, CES-D= Centers for Epidemiologic Studies

Depression Scale; PASE= Physical Activity Scale for the Elderly; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; CSQ= Coping Strategies Questionnaire

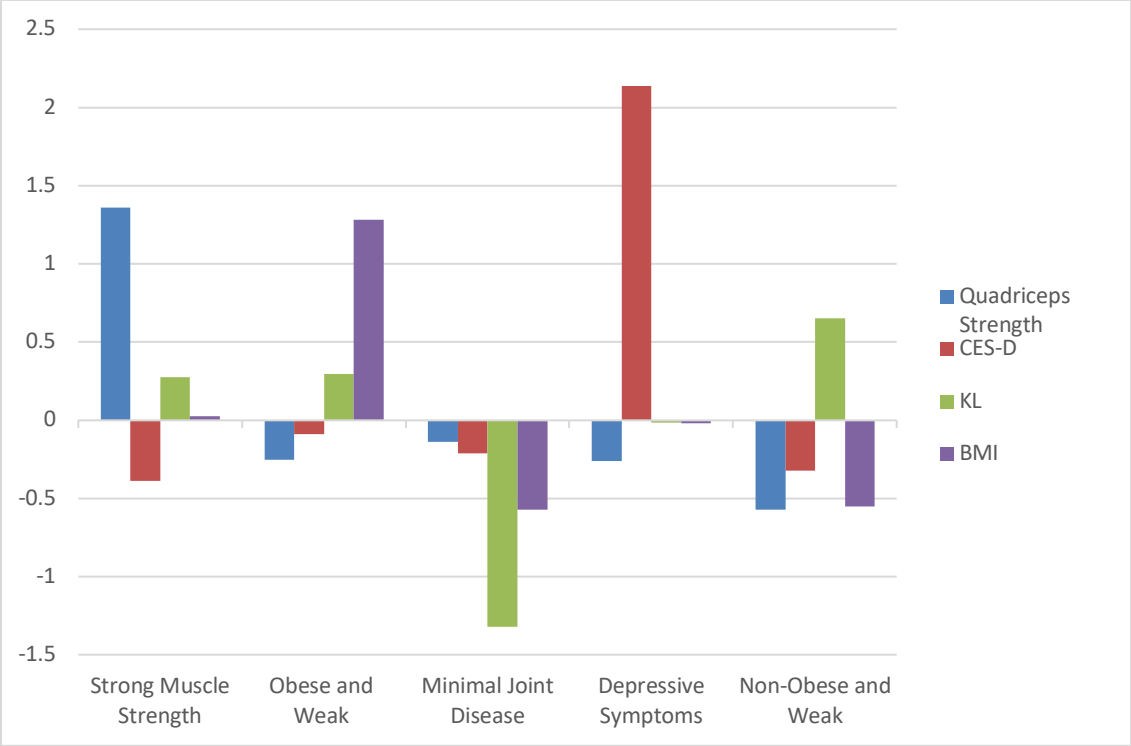

Figure 2.

K-Mean Cluster Centers Using the Standardized Z-Score Values for Quadriceps Strength, CES-D, KL and BMI in each cluster.

Abbreviations: KL= Kellgren and Lawrence Score BMI= Body Mass Index, CES-D=

Centers for Epidemiologic Studies Depression Scale.

Table 6.

Descriptive Information of Clusters (N= 1057)

	Strong Muscle Strength (n= 205)	Obese and Weak (n= 220)	Minimal Joint Disease (n= 250)	Depressive Symptoms (n=99)	Non-Obese and Weak (n= 306)
Radiographic OA, %					
KL-0	5.4	4.1	69.1	15.0	0
KL-1	14.6	10.0	30.9	14.0	0
KL-2	36.1	39.5	0	41.0	41.6
KL-3	28.3	37.7	0	19.0	34.8
KL-4	15.6	8.6	0	11.0	23.6
Strength (N)	349.8± 72.1	202.5 ± 61.5	212.9± 68.7	201.7 ± 78.4	173.3 ± 53.0
BMI (kg/m^2)	29.7 ± 3.2	35.8 ± 3.2	26.8 ± 3.5	29.5 ± 4.9	26.9 ± 3.0
Obese %	47.3	100.0	18.6	45	17.5
CES-D Score	4.3 ± 3.9	6.5 ± 5.1	5.6 ± 4.8	23.2 ± 5.8	4.8 ± 4.1
CES-D >16, %	0.5	8.2	3.7	95	0.3

Table values are mean ± standard deviations or % Abbreviations: KL= Kellgren and Lawrence Score BMI= Body Mass Index, CES-D= Centers for Epidemiologic Studies Depression Scale.

Table 7.

Means of Select Clinical Measures By Phenotypes.

	Strong Muscle Strength	Obese and Weak	Minimal Joint Disease	Depressive Symptoms	Non-Obese and Weak
PASE Score	183.4[a]	145.2 [b, c]	167.2 [a, b]	143.3 [c]	145.6[b, c]
400 Walk (s)	289.9 [a]	334.1 [b]	303.4 [a]	324.8 [b]	320.9 [b]
Charlson Comorbidity Score	0.4 [a]	0.7 [b]	0.5 [a]	0.7 [b]	0.5 [a]
WOMAC Pain Score	2.7 [a, b]	3.8 [c]	2.5 [a]	4.8 [d]	3.2 [b, c]
CSQ Catastrophizing Score	0.5 [a]	0.7 [a]	0.6 [a]	1.7 [b]	0.7 [a]
CSQ Divert Attention Score	0.8 [a]	1.3 [b]	1.2 [a, b]	1.4 [b]	1.3 [b]

Homogeneous subsets from a Tukey's HSD Post Hoc Test are described using the superscript letters. NOTE: * Means with the same letter for each clinical outcome are not statistically different

Abbreviations: PASE= Physical Activity Scale for the Elderly; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index; CSQ= Coping Strategies Questionnaire

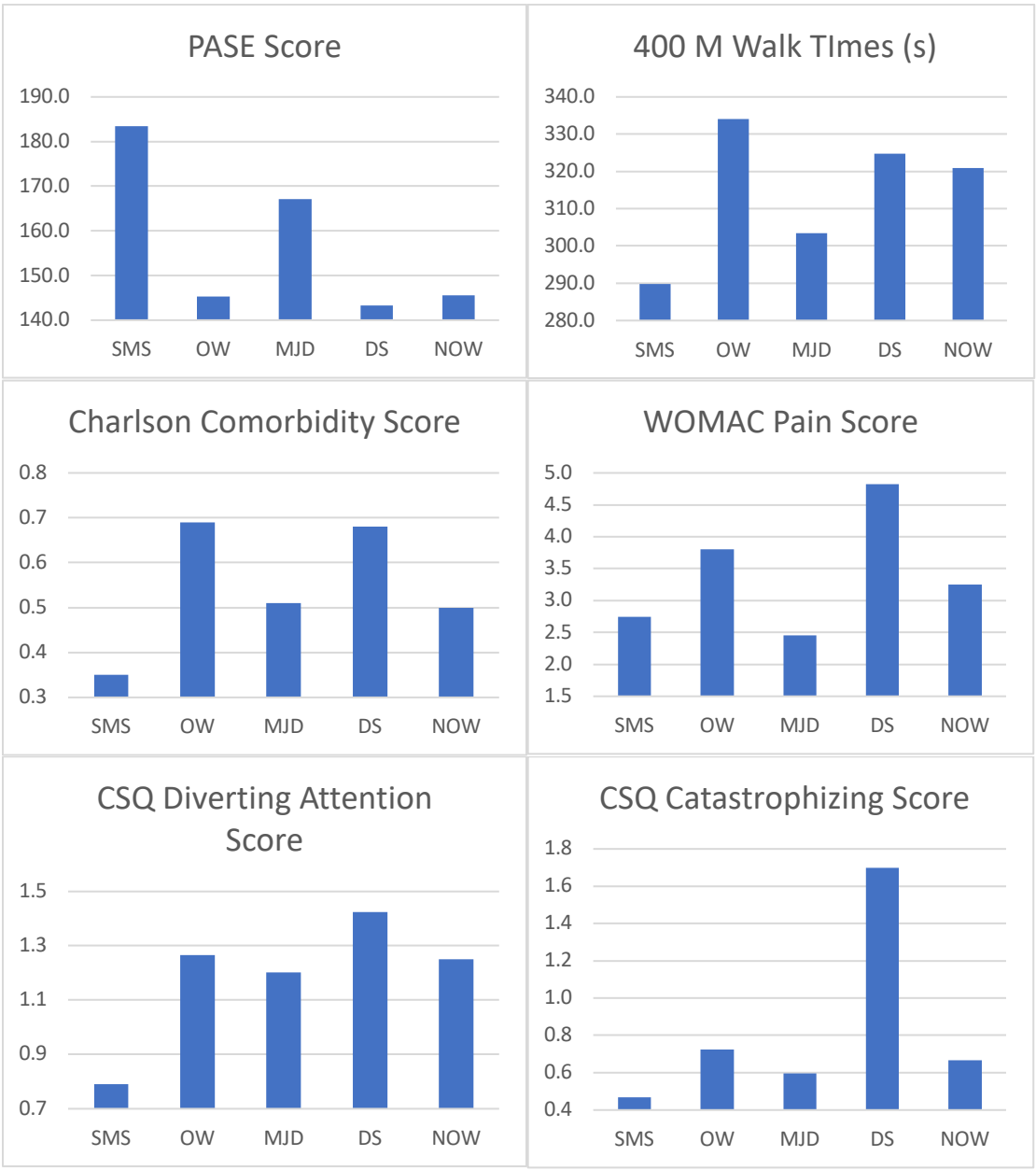

Figure 3.

Mean Scores for Select Clinical Outcome Measures by Phenotype.

Abbreviations: SMS= Strong Muscle Strength, OW= Obese and Weak, MJD= Minimal Joint Disease, DS=Depressive Symptoms, NOW= Non-Obese and Weak

Chapter IV

CONCLUSION

It has been reported that about 50% of healthy adults do not meet national guidelines for daily physical activity. As adults age, this number becomes more pronounced, particularly in older adults with chronic conditions, such as knee OA.[1] Knee osteoarthritis as a disease entity itself often results in mobility limitations, making participation in physical activity challenging: however, performing activity to tolerance can be beneficial, even at light intensities.[2,3] The two primary aims of this dissertation were: 1) to examine how various physical, psychological, and general health factors influence physical activity in individuals with knee osteoarthritis; and 2) to identify clinical phenotypes in a population of individuals with knee osteoarthritis and their associated functional outcomes, including physical activity. Insights gained from these two studies have the potential to impact the conservative approach to treatment for a large segment of the American population with osteoarthritis.

Literature suggests that there is an association between increasing volumes of moderate to vigorous physical activity and the reduction in disability and all cause morbidity and mortality rates. [4-6] Loprinzi et al suggest that if older adults with mobility limitations increased the amount of time they participated in light physical activity, their rate ratio of chronic diseases would decrease.[7] To combat the sequelae of chronic disease, it is important for the health care community to focus on getting this population much more physically active earlier.[3]

As the 2018 Physical Activity Guidelines Advisory Committee suggested, preventing chronic disease and maintaining functional independence has significant public health implications.[3] Therefore in the first study, we decided to examine the associations between self-reported psychological, functional and health related outcomes including coping strategies and total physical activity time, as measured by accelerometry, in adults between the age of 45- 79 years old with knee osteoarthritis.

In order to complete this work, we utilized the Osteoarthritis Initiative, which is a publicly and privately funded longitudinal multicenter study examining the onset and progression of knee osteoarthritis. We looked at significant correlates (sociodemographic, psychological, functional and health related measures) of total physical activity time to estimate total PA using a linear regression model with bootstrapped standard errors.

Our results report that over three-quarters of individuals examined in this study did not meet recommended volumes of daily physical activity. We identified 4 major factors associated with total physical activity levels in a population with mild to moderate knee OA: co-morbidities, age, BMI, and the diverting attention coping strategy. The final adjusted R^2 value for the model used in our first study was 0.22, suggesting that other factors may play a role in the association of physical activity not mentioned in our study. Because knee osteoarthritis presents in such a varied population, our second study aims to describe different clusters, or phenotypes, of people with knee osteoarthritis and understand differences in their clinical outcomes.

After completing the first study and recognizing how much variability was not explained by the resultant model, we decided to look at this further. In reviewing the literature, we found previous studies that identified distinct phenotypes, or sub-categories

of individuals with knee osteoarthritis. We questioned whether this might provide additional insight into the range of outcomes in individuals with knee osteoarthritis. First, we wanted to understand if phenotypes existed in this population and if so, how might they differentially impact clinical outcomes and therefore possible approaches to intervention. This led me to the purposes of my second paper, which were to: 1) to identify clinical phenotypes described in the literature in a population of the OAI; 2) to examine and compare clinical outcomes including physical activity, functional mobility, pain, coping strategies and comorbidities among phenotypes.

Identifying phenotypes of people with knee osteoarthritis may help better target interventions to optimize physical activity and to enhance functional outcomes.
To answer these questions, we completed a cluster analysis using a sample of 1057 of individuals with knee osteoarthritis from the OAI data base between 2008-2010.

In the second study of this dissertation, we reported 5 clinical phenotypes in people with knee osteoarthritis consistent with the literature: Strong Muscle Strength, Minimal Joint Disease, Non-Obese and Weak, Obese and Weak and Depressive Symptoms. We also reported significant differences in clinical measures between groups. The groups with the highest levels of physical activity are the Strong Muscle Strength and Minimal Joint Disease Phenotypes. The highest levels of physical activity and function were noted in the Strong Muscle Strength and Minimal Joint Disease Phenotypes; while the lowest scores for all outcome measures were reported in the Depressive Symptoms Phenotype. Although certain risk factors for developing OA are not modifiable, others lifestyle factors, such as weight management, physical activity,

muscle strengthening exercises and addressing depressive symptoms can play a significant role in modifying the risk, progression and symptoms of knee OA.

Future Recommendations

Based on the results of these studies, we suggest 1) refinement of the phenotypes in knee osteoarthritis utilizing a broad population; 2) identifying targeted interventions based on these phenotypes; 3) identifying different phenotypes of people related to physical activity behavior to be able to better target interventions; 4) determine short and long term impact of these targeted interventions and 5) Understand the longitudinal effect of physical activity and function on knee osteoarthritis. It is also important to study what we have learned retrospectively, to formulate enhanced randomized controlled trials for the treatment of people with knee osteoarthritis.

As we know, knee osteoarthritis is a complex multifactorial health condition that is progressive in nature and often presents with multiple co-morbid conditions, as well as decreases in physical activity, significant health related decline and functional deterioration. Incorporating and encouraging individuals to participate in any level of physical activity may have significant public health implications including reducing long-term disability, mortality, and morbidity; however more research is warranted to more fully understand these relationships across the lifecycle of individuals with OA.

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Appendix A

Review of Literature

Osteoarthritis Introduction

Prevalence and Incidence

The National Health Interview Survey (NIHS) is a survey that is conducted to collect information on self-reported health status. The NHIS asks two questions about arthritis: “have you ever been told by a doctor or other health care professional that you have some form of arthritis?” and “are you now limited in any way in any of your usual activities because of arthritis or joint symptoms?” The NIHS reports that Arthritis is one of the most common causes of disability in adults over 60 years of age.[1] From the surveys performed in 2003-2005, the prevalence of arthritis was estimated to be 21.6% or 47.8 million people in the United States.[2] Projections suggest that the prevalence of arthritis is expected to rise to 67 million people by 2030. In a recent paper by Hootman et al in 2016 based on data from the NHIS survey, it is projected that by 2040, 25.9% of the population or 78.4 million individuals, will have a diagnosis of arthritis.[1] The high prevalence of OA creates a burden on the health care system requiring understanding in proper treatment and care for this large population.[3]

Osteoarthritis, one form of arthritis, results in a higher incidence of mobility disability than any other chronic condition, and it is most commonly found in the knee.[4,5] Knee osteoarthritis is estimated to affect over 14 million adults in the United States.[6]

Osteoarthritis can be assessed through symptomatology or radiographic evidence of disease progression. In determining prevalence and incidence, varying application of these criteria is in part why there are many differing estimations of incidence and prevalence of this disease. Multiple longitudinal surveys and studies of the US population describe different prevalence throughout the country. The Johnston Country Osteoarthritis Survey looked at about 3000 adults over the age of 45 years old in rural North Carolina and reported the prevalence of radiographic knee osteoarthritis as high as 27.8% in adults over 45 years old.[7] In the Framingham Osteoarthritis study, 2400 participants in suburban Massachusetts over the age of 65 report prevalence of 15% radiographic OA and 9% symptomatically.[8] In the National Information Health Survey, prevalence was categorized by age, gender and obesity and ranged from .4 to 34%, the highest being overweight women over the age of 74. The incidence of OA peaked between 50 and 65 and the mean age at diagnosis was 53.5 years of age. Differences in these results can be due to age, radiographic vs symptomatology for diagnosis, location (urban vs. rural) and race. No matter the exact number, we do know this is a growing concern globally.

The most recent data on incidence and age of onset of symptomatic knee osteoarthritis utilized self-reported data from the National Health Interview Survey in all adults over the age of 25 years. Incidence of symptomatic knee osteoarthritis peaked at

age 55-64 years, with a mean age at diagnosis of 53.5 years of age, higher in women and obese individuals.[9]

Health Care Costs

Osteoarthritis is ranked as the 11th highest contributor to disability out of 291 conditions studied across 187 countries in 2010. [10] In the United States, osteoarthritis has been reported to cost the health care system more than 128 billion dollars per year (81 billion in direct medical costs and 43 billion in lost earnings).[11] On average, for each person diagnosed with osteoarthritis direct medical costs are $129,600 per lifetime.[12] These costs are expected to increase as the population, including the baby boomer generation, ages and becomes more obese.[13] Osteoarthritis typically affects middle aged to older individuals and can create an economic burden as a result of lost time at work and early retirement[14], in addition to an estimated $12,400 in direct medical costs per person.[12] The total economic cost for arthritis has been estimated to exceed 2% of the US gross domestic product.[14] Not only does osteoarthritis itself increase health care costs, it has also been linked to metabolic and systemic conditions such as hypertension, hypercholesterolemia and high blood glucose levels, which can lead to larger health implications and further economic burdens.[15-17].

Osteoarthritis Pathology

Although described as a degenerative joint disease, OA affects all structures within and around the joint, including the cartilage, underlying bone, joint capsule,

surrounding muscles, tendons and ligaments.[14,18,19] Loss of articular cartilage, which is made up of collagen and proteoglycans, is the primary progressive pathologic change seen in osteoarthritis.[20] Articular cartilage provides a low friction smooth surface for transmission of loads across joints and allows for proper shock absorption.[21] In the early stages of osteoarthritis, irregularities and fibrillations, or vertical fissures, develop along the surface of the cartilage. Over time, these irregularities extend deep into the subchondral bone and start to expose the bone to the joint surface. Focal loss of cartilage can create increased areas of pressure and stress along the joint, which furthers the progression of cartilage loss.[19] At a cellular level, chondrocyte function begins to break down and reduce its ability to repair the cartilage matrix over time, known as "chondroseniscence".[21] Pro-inflammatory cytokines and matrix degrading enzymes are produced that further the breakdown of cartilage; rather than assist in its repair.[22]

As osteoarthritis progresses into the later stages, changes occur along the subchondral bone. Cysts begin to form, and the subchondral plate thickens with a less flexible connective tissue creating a stiffer surface that is less shock absorbent. Progressive remodeling causes osteophyte formation or the formation of bony outgrowths at the joint margins.[22] Very often, these bony changes are the cause of pain in patients with osteoarthritis because of the stretching and lifting of the bony periosteum that occurs during this remodeling.[5]

The joint synovium also influences the progression of osteoarthritis. The joint synovium is important in producing hyaluronate, which is a viscoelastic fluid that aids in reducing friction and absorbing shock in the knee joint. This fluid is critical in the maintenance of joint health as it protects against inflammatory cells and nociceptors.[20] As

osteophytes form, the synovium itself becomes inflamed and goes through a process of hyperplasia and fibrosis.[5] The synovium is no longer able to maintain its role in joint protection and starts to release proinflammatory cytokines such as interleukin 1, interleukin 6, and tumor necrosis factor alpha, which further contribute to cartilage breakdown and osteoarthritis progression.[20]

As the joint space narrows and the capsule begins to stretch, laxity is present in the medial or lateral collateral ligaments. A feeling of the knee buckling or "giving way" is commonly noted by patients with knee osteoarthritis, which is independently associated with quadriceps muscle weakness.[14,23, 24] Because of capsular swelling around the joint, arthrogenous muscle inhibition of the quadriceps muscle can lead to weakness, further pain and degeneration.[19,25] In a longitudinal study using the MOST (Multicenter Osteoarthritis Study) cohort, quadriceps strength was not associated with radiographic evidence of knee osteoarthritis, however, increased quadriceps strength has been reported to be protective against symptomatic knee osteoarthritis and is critical in rehabilitation of the painful knee.[19,26]

Osteoarthritis Diagnosis

Osteoarthritis is diagnosed using both physical signs present on x-rays and symptomatlogy.[27] On radiographs, OA is consistent with a progressive loss of hyaline cartilage, marginal outgrowths, osteophyte development, joint space narrowing, subchondral sclerosis, and subchondral cysts.[4,28,29] Radiologists have developed the Kellgren-Lawrence Scale to maintain consistency in measuring the progression of

osteoarthritis via radiographs. This scale is widely used to determine the extent of marginal outgrowths of osteophytes.[30]

Many individuals with radiographic changes are asymptomatic, thus, a diagnosis often occurs only after the patient becomes symptomatic. Symptoms can include morning pain and stiffness that improves after 30 minutes of waking; pain or crepitus after walking long distances, getting in and out of a chair, going up and down stairs or squatting down to the floor; joint line tenderness; range of motion limitations; the feeling of instability; joint effusion and deformity.[4,31] Very often, the signs and symptoms of osteoarthritis prevent patients from participating in recommended daily physical activity.

Osteoarthritis: Intrinsic and Extrinsic Risk Factors

The causes of osteoarthritis are multifactorial. These factors can be divided into intrinsic factors, such as age, genetics, gender, and extrinsic factors, such as obesity, prior injuries related to occupational and sport activities, joint overload and physical activity levels.[28, 32]

OA is significantly associated with age as incidence and prevalence of osteoarthritis increases 2 to 10-fold between the ages of 30-65 years, leveling off by the age of 80 years. Osteoarthritis is more common in men before the age of 45 years, potentially due to occupation or sport and leisure participation. [28,33] Over the age of 45 years, women have a higher incidence of osteoarthritis.[15,34] Some researchers postulate this is due to the changes in levels of estrogen and bone density resulting from the

hormonal changes occurring at menopause; however the exact mechanism is still debated.[20,35]

There is a genetic link found in the development of osteoarthritis. In studies looking at hereditary traits in twins, osteoarthritis has been linked significantly to osteophyte development, cartilage volume and radiographic progression of osteoarthritis.[36,37] Other studies have found links between osteoarthritis and the X chromosome, as well as chromosome 2, 4 and 16.[38] Although the factors described above are not modifiable (as gene therapy is still in its infancy), other extrinsic risk factors are; such as prior injury, vocation, obesity, and physical activity levels are modifiable factors.[39]

Repetitive, high impact, torsional joint loading sports such as football or soccer may increase the risk of developing OA.[29,40,41] In a study of professional soccer players, football players and runners, those who participated in higher impact twisting and pivoting sports had a higher likelihood of developing osteoarthritis compared to those participating in running, which is a linear sport.[40] Similarly, certain occupations such as house cleaners, dock workers, or construction workers require persistent kneeling, repetitive deep squatting, or heavy lifting can increase the risk of developing OA.[28,40,42] A German case-control study of men and women to identify risk factors for osteoarthritis, demonstrated that there is a higher dose-response relationship between kneeling and squatting and the development of symptomatic knee osteoarthritis.[42]

Prior injuries to the knee joint, including ligaments, tendons and muscles, can increase the risk of knee osteoarthritis.[43] [27,34] About half of all patients who have had ACL or meniscus injuries go on to having painful osteoarthritis 10-20 years later.[44] This

is becoming a larger portion of OA patients, because ACL injuries are more common in a younger people, especially in young athletes.[45] Altered joint mechanics from poor muscular strength, varus or valgus alignment, decreased proprioception or joint laxity potentially can increase risk of osteoarthritis.[4,28,44]

The risk of osteoarthritis increases significantly as body mass index increases.[39,46,47] The Rotterdam Study examined radiographs of 3,585 adults over the age of 55 years and reported an increase in osteoarthritis of the knee as body mass index increases.[46] Not only does the risk of osteoarthritis increase with increased body weight, so too does the risk of disease progression.[39] Joint biomechanics change with higher body weight, altering articular cartilage loading surfaces.[48] For example, there is a 2-3 pound increase in forces across the knee joint while standing on one foot for each pound of weight gain [28,49]

Although certain risk factors for developing osteoarthritis are not modifiable, others lifestyle factors, such as weight management, physical activity, and muscle strengthening exercise can play a significant role in modifying the risk of arthritis. Treatment of painful osteoarthritis has been proven effective using a program of both diet and exercise.[4,50,51] Physical activity does not only reduce painful knee osteoarthritis symptoms; it also has significant impact on all cause morbidity and mortality rates.[52,53]

Osteoarthritis and Pain

Epidemiologic studies suggest that half of those patients presenting with positive radiographic findings of OA report little to no pain; while other patients with minimal to

no radiographic evidence report significant pain.[20,54] This may imply that factors other than the actual physical processes described above may influence patients' pain experience.[55,56]

Two types of pain are present in patients with osteoarthritis; dull, achy, consistent background pain and sharp, intense, intermittent pain. The type of pain that most impacts patient quality of life, is the sharp, intense intermittent pain.[57,58] As osteoarthritis progresses from early stages to later stages, sharp pain becomes more constant and can be draining on patients, leading to activity avoidance and passive coping strategies.[56]

Because of the wide variability in how patients with osteoarthritis present, recent research trends have shifted toward the examination of differences in patients' pain experiences versus the traditional focus of investigation on anatomy and pathophysiology alone.[55,59] Current research on central sensitization of pain and psychological distress has the potential to significantly impact available treatment strategies and enhance patient quality of life.[55]

Central sensitization is a maladaptive change to the sensory processing system influencing multiple levels of the nervous system including the spinal cord, brain stem, thalamus, sensory and motor cortex, prefrontal cortex, cingulate cortex and limbic system.[55] Patients with central sensitization present with symptoms such as hyperalgesia and widespread decreases in their threshold for pain, pressure, and mechanical stimuli throughout their entire body, not just a specific joint or area.[60] Central sensitization has been reported to influence some patients with knee pain associated with osteoarthritis, which can pose a challenge for treatment.[60,61]

Finan et al (2014) categorized patients into groups with high and low radiographic evidence of osteoarthritis as well as high and low levels of pain, creating four subgroups of patients. Patients with high pain and low radiographic evidence of osteoarthritis report a higher risk of developing central sensitization due to hypersensitivity to qualitative sensory testing in areas distal to the knee. They also have significantly greater pain catastrophizing, depression, and anxiety as compared to the patients presenting with low levels of pain and high levels of radiographic osteoarthritis.[60]

Psychological distress can be assessed though multiple measures such as self-efficacy, depression, anxiety, and fear. These factors not only influence the psychological wellbeing of patients with osteoarthritis, they also influence measures of physical function and disability.[56,59,62-64]

Using a cross sectional sample of 3,494 patients from the Osteoarthritis Initiative database, Kittelson et al (2014) aimed to determine pain phenotypes in patients with osteoarthritis.[59] Based on latent class modeling, participants were categorized into to 1 of 4 distinct classes. Class 1 patients had the highest number of comorbidities, Class 2 patients had higher frequency of knee joint tenderness, Class 3 patients had higher levels of psychological distress and number of pain sites, and Class 4 patients had lower radiographic evidence of OA, little psychological distress and greater strength. Ten percent of the study population was categorized as Class 3 patients and these patients sought health care services for osteoarthritis at higher rates than most other participants. Class 3 patients also present with the greatest level of disability and significantly higher levels of pain, linking psychological distress to poorer health outcomes for patients with osteoarthritis, potentially through mechanisms such as passive coping strategies and

activity avoidance.[59] Recognizing patients with higher levels of psychological distress and number of pain sites (i.e. Class 3) are more likely to seek medical attention and add to the cost burden of care may lead to an expansion of treatment options beyond the management of musculoskeletal dysfunction.

Coping with Osteoarthritis

Many factors influence patient perceptions of pain, including patient thoughts, beliefs, and reactions to pain, and a patient's coping strategies.[65,66,54] Lazarus and Folkman described the Transactional Theory of Stress and Coping as consisting of three processes, primary appraisal, secondary appraisal and coping.[67] Primary or cognitive appraisal, consists of determining nature of the situation and if the stressor is a threat to the individual. Secondary appraisal involves deciding whether there is anything the individual can do to change the current situation or respond to the threat. Coping strategies are responses to the interaction between the primary and secondary threat appraisals. [68,69] For example, if a person believes there is a threat; yet there is nothing they can do to change the situation, they may cope differently than if they believed there was a possibility of changing the outcome.

Coping strategies are defined based on a persons' perception of how much control they have over the situation. Coping strategies have been divided into active or problem focused coping strategies and passive or emotion focused coping strategies.[70,71,72]

Active coping strategies facilitate adaptive steps to manage, remove, or problem-solve the stressful situation.[69] For example, patients who have knee osteoarthritis may use self-statements such as, "I can not let pain get in the way of what I have to do" or, "I see

it as a challenge and don't let it bother me".[73] As reported by Regier (2015), patients with knee osteoarthritis who practice more active coping strategies seem to have less disability and better physical function compared to patients who engage in more passive coping strategies.[72] In a study examining discrepancies between radiographic evidence of osteoarthritis and functional limitations in osteoarthritis, patients with higher radiographic evidence of osteoarthritis who use active coping strategies such as positive self-statements have higher functional mobility compared to those who use passive strategies.[54]

Passive, or emotion focused coping strategies, are considered maladaptive strategies in which individuals tend to depend on others for help rather than taking ownership over their current situation to depend on others for help.[70,71] This disengaged strategy is identified with depression, physical disability and helplessness.[69,71] Patients with long standing chronic pain report using passive coping strategies more consistently, which has a greater impact on functional limitation and pain compared to active strategies.[70] In patients with rheumatoid arthritis, it has also been reported that physical disability and the use of passive coping strategies are significant predictors of pain.[71]

One example of a maladaptive methods of coping is pain catastrophising.[54] Pain catastrophising has been defined as a magnified emotional focus on pain sensations and a feeling of helplessness in the face of pain.[74] Pain catastrophising has been reported to be associated with a higher level of pain and disability and slower walking speeds.[74] Because of these maladaptive strategies and helpless nature, these individuals may be limited in their ability to engage in physical activity,[74] however the link between specific

coping strategies and their influence on physical activity behaviors in patients with osteoarthritis are missing in the literature.

There are few prospective longitudinal studies investigating coping strategies in patients with osteoarthritis as predictors of health outcomes.[75] This information can give insight into the influence of coping strategies on behavior for clinicians to influence patient care.

Measurement of Coping Strategies

Coping Strategies are measured in many ways. One of the most widely used methods to describe coping strategies is the Coping Strategies Questionnaire. This internally valid questionnaire was developed using a sample of patients with low back pain.[76] It was developed as a 50 item questionnaire to measure 6 cognitive coping strategies that people use while they have pain, and 2 behavioral strategies related to how people act while they have pain (i.e., praying or hoping, reinterpreting pain sensations, pain catastrophizing, coping self-statements diverting attention, ignoring sensations, increased behavioral activity and ignoring pain sensations). The scale is measured using a 7-point Likert scale rating how often the participant uses the strategy while they are in pain from no use to frequent use.[76]

Because of the length of this questionnaire, and potential burden to participants, this scale was later validated using a truncated 14-point scale with two questions per construct.[77,78] This version was further validated in a population of older adults with chronic pain[70], and knee osteoarthritis pain.[78] Riddle and Jensen (2013) believe the use of

the Coping Strategies Questionnaire is an advantageous component of the patient assessment to assist clinicians in managing patients with poor coping strategies.[78]

Coping Self-Management Programs and Osteoarthritis

Encouraging active coping strategies is an important component of self-management programs, which along with exercise, are strongly recommended as the conservative approach to knee osteoarthritis from the American Academy of Orthopedic Surgeons.[79] Self-management programs alone have been reported to improve pain, quality of life, and function using skills such as problem solving, imagery, goal-setting and cognitive behavior therapy.[80] The Osteoarthritis Knee Self-Management Program (OAK) and the Stanford University Arthritis Self-Management Program (ASMP) are two osteoarthritis-specific self-management programs designed to promote behavior change in people with knee osteoarthritis, with positive results.[80] Both programs focus on self-management, but do not have a physical activity component included in their interventions, however, multiple studies have reported exercise is more beneficial than patient education programs alone, which is why continued research on the relationship between coping strategies and physical activity is important.[81] [82]

The Enabling Self-management and Coping with Arthritic Knee Pain through Exercise (ESCAPE) program was designed to improve function, understanding of the disease process, and confidence by combining education, advice, reassurance, and simple coping strategies along with performing supervised exercises.[83] This program included an individualized progressive exercise program and an education-based self-management

program. A randomized control trial compared standard primary care interventions to the ESCAPE program and a six-month follow up study noted improved function with the ESCAPE intervention program.[83]

A significant limitation to the combined exercise and patient self-management programs are the costs associated with treatments. A randomized control trial by Bennell et al (2016) was completed with three groups: exercise alone, self-management alone and exercise plus self-management.[84] The results demonstrated a significant improvement in both groups for one year. Self-management programs addressed more psychological variables studied, where the exercise intervention influenced more physical outcomes. The greatest improvements across both physical and psychological variables were noted in the combined treatment group, however the costs analysis suggested that the cost of delivery did not offset the significant savings due to longer sessions.[84]

This study did report success with physical therapists, in lieu of psychologists, to deliver self-management interventions as well as exercise interventions.[84] This provides rationale for physical therapists to incorporate education of patient coping strategies including pain coping skills such as active rest cycling, developing coping thoughts, pleasant imagery and problem-solving into their current exercise and physical activity treatment plan for improved patient care.

According to the NIH conference in 2000, socio-behavioral interventions have continually been an underutilized form of therapy for treatment of osteoarthritis, where less than 2% of the US population with osteoarthritis population participates[23]. Combining cognitive behavioral interventions with a physical therapy can have a large impact on treatment of this disease, but first, a better understanding of the physical,

cognitive and behavioral factors interacting with physical activity and mobility loss must be explored.

Avoidance Model

Avoidance of activities is considered a passive coping strategy that can promote disability and functional limitations in patients with chronic pain, including osteoarthritis.[85] Chronic musculoskeletal disorders have been associated with avoidance of activity due to catastrophizing or a feeling of helplessness in the face of pain, which is also associated with functional decline.[86]

The avoidance model can be described using the translational model of stress and coping, which postulates that the primary appraisal is the experience of pain patients with osteoarthritis feel with activity as a threat. Secondary appraisal of how people respond to this pain, and this case, it is using a coping strategy of avoidance to reduce the pain.[67,86] Although activity avoidance may have the desired short-term effect of decreasing pain, in the long term, this can lead to inactivity, and decreased fitness and muscular strength.[66] This concomitant decrease in fitness and strength can worsen symptoms of osteoarthritis, reinforcing a cycle resulting in increased pain.

Holla et al. concluded that there is strong evidence to support the relationship between avoidance of activities and muscular weakness with subsequent activity limitations.[87] A 5-year longitudinal prospective cohort reports a partial association between avoidance of activities and poorer knee extensor strength and greater functional limitations. Although the longitudinal component of this study was not able to

demonstrate causation, it confirmed greater avoidance over time is also associated with greater muscular weakness.[88]

There are weaker associations between pain and psychological distress leading to avoidance of activities. The Cohort Hip and Cohort Knee (CHECK) is a prospective longitudinal study of knee and hip osteoarthritis progression in the Netherlands of 1,002 participants over 10 years.[89] In the CHECK cohort, negative affect, or psychological distress, is associated with muscular weakness and mediated by avoidance of activities. They also report an association between pain and muscular weakness, mediated by activity avoidance.[90]

In a 5-year follow up of this same cohort, avoidance of activities due to pain predicts greater activity limitations due to muscular weakness and deconditioning continuing to give validity to the avoidance model.[91] The biggest limitation to the CHECK cohort is the use of self-report questionnaires for all of their data collection. Recall bias and the subjective nature of questionnaires limit accuracy of responses; so further research in this area using objective data, such as accelerometry would further enhance our knowledge of this model.[91]

Along with activity limitations providing a significant impact on global health of individuals with osteoarthritis, physical inactivity is also a significant health variable and should also be considered when looking at the avoidance model.

Physical Activity Measurement

Physical activity is defined as “any movement of the human body by the skeletal muscles that expend energy”.[92] Such variability of movement in free-living environments makes measuring physical activity challenging.[93] There are two main methods of measuring physical activity behavior: self-report questionnaires and instrumented measurement physical activity through the use of accelerometers.

Self-report questionnaires are one of the most commonly utilized methods of measuring physical activity behavior. They allow easy and practical analysis of large groups of participants with low burden and low cost to both the participants and researchers.[93] It also can give an understanding of the participant’s beliefs, expectations and perceptions surrounding physical activity.

These methods do not come without limitations. Very often through questionnaires, physical activity is either over or underestimated.[94] Not all surveys capture total physical activity including unplanned behaviors, household activities such as cleaning around the house, or short bouts of low intensity physical activity. [95] There is also significant reporting bias due to social desirability and difficulties of recall, especially in older adults.[94,96,97] It is because of these reasons that instrumentd monitoring of physical activity through the use of accelerometers is becoming increasingly more popular.

Accelerometers quantify physical activity, and approximate an individual’s energy expenditure, through assessment of movement of the human body.[98] These sensors, most commonly piezoelectric sensors are used to measure acceleration and are

recorded as voltage signals.[98] The higher the amplitude of the voltage signal, the higher the acceleration of the person is detected. Data output contains raw acceleration signals, or activity counts that can be analyzed to determine the amount of movement. [99] Based on these counts, specific thresholds, or cut points have been created that identify sedentary, light, moderate or vigorous physical activity. This allows researchers to understand total physical activity behavior as well as if participants are meeting the recommended physical activity guidelines.

The National Health And Nutrition Examination Study (NHANES) in 2003-2004 procured the first nationally representative sample of the United States population including accelerometry data with support from the National Cancer Institute of the National Institutes of Health.[96] Using these data, Troiano et al. looked at physical activity in the United States.[96] Results demonstrate that children participate in about 1 hour per day of moderate physical activity, but this physical activity time decreased steadily as the population aged. Adults over the age of 60 years performed only 6-10 minutes of moderate to vigorous physical activity per day.

In older adults, the use of accelerometers has been utilized and determined a practical and valid method for gaining insight into physical activity behavior.[97,100] Harris et al. performed a cross sectional study looking at physical activity levels in older adults using accelerometers. They reported increasing age, poor health, disability, diabetes, higher BMI as well as low exercise self efficacy and low perceived exercise control were all significantly associated with lower physical activity counts measured by accelerometer.[101]

A systematic review and meta-analysis by Hupin et al. in adults over the age of 60 years, report a 28% reduction in risk of all-cause mortality for individuals who meet physical activity guideline. It also reports that those who participate in low levels of moderate to vigorous physical activity also have a significant reduction in all-cause mortality (22%) compared to those who do not participate in any physical activity.[52] This is important to understand that even lower doses of physical activity have a place in preventive medicine. Compared to individuals without disabilities, those with mobility disability participate in greater amounts of sedentary behaviors and lower numbers of light and moderate physical activity, as well as presenting with poorer biomarker levels including BMI, triglycerides, Hb_{A1C} and homocysteine. Understanding the importance of light physical activity can help create activity guidelines for people who may not be able to tolerate the desired amounts of moderate to vigorous activities due to chronic illness or pain.

Light physical activity makes up a majority of the amount of physical activity performed by people in each day, including shopping, daily care, errands and walking.[102] Self report of light physical activity can be difficult, thus the use of instrumented measurements of physical activity provides researchers more accurate measurements of light physical activity as well as moderate to vigorous activity.[103, 102] Further studies using data from the National Health and Nutrition Examination Survey (NHANES) report that physical activity, even at light intensity may improve cardiovascular health and decrease mortality risk.[104] Most recently, the Physical Activity Guidelines Advisory Committee suggested that any amount of PA is beneficial, even at light intensity.[105] PA of all intensities can result in health benefits and should be recommended for individuals

with OA who are unable or unwilling to engage in greater amounts of PA due to possible mobility limitations.

In looking at combined light, moderate and vigorous physical activity time, there is evidence to support that total physical activity time is another variable to help understand how physical activity influences health. In a study by Loprinzi et al, the individuals with the lowest total volume of physical activity time per day were significantly older and presented with greater prevalence of chronic disease than those with greater levels of total activity.[102] Loprinzi also reported that those with the higher total volume of physical activity had significantly lower mortality rates than those with the lowest levels of total physical activity.

Physical Activity in Older Adults with Osteoarthritis

Older adults with knee osteoarthritis often experience physical inactivity, which is a leading factor in functional decline.[106] The American College of Sports Medicine recommends all adults participate in 150 minutes of moderate or 75 minutes of vigorous physical activity per week.[107] As compared to adults without osteoarthritis, those with osteoarthritis are insufficiently physically active and are less likely to meet the recommended targets of physical activity.[66,108]

White et al. used the MOST database to look at 1788 patients with knee osteoarthritis. They discovered that about 16% of males and 12% of females are meeting the 10,000 step recommendations, however, when looking at the guidelines for intensity set forth by the Department of health and Human Services PA guidelines in 2008, only 6% males and 5% of females are meeting those recommendations.[109] In a similar

population of adults with knee osteoarthritis Dunlop used the Osteoarthritis initiative database and reported 13% of males and 7% of females meeting those same aerobic guidelines.[110] They also reported that about 40% of males and 56% of females participated in no bouts of moderate to vigorous physical activity greater than 10 minutes over the course of the 7 days measurements.

Farr et al. compared individuals with end-stage knee osteoarthritis to control individuals and found self-reported physical activity was 60% less, walking speed was 30% slower and perceived disability, pain and stiffness was significantly greater in patients with knee osteoarthritis.[111] This is consistent with De Groot et al who reported a 19-27% difference in physical activity between patients with end stage hip and knee osteoarthritis and healthy controls.[108] In a study of individuals with early stages of knee osteoarthritis, 70% of participants did not meet recommended daily levels of physical activity measured by accelerometer.[112]

Regular physical activity for individuals with knee osteoarthritis is essential not only for cardiovascular risk reduction and overall health, but also for pain and stiffness reduction, maintenance of muscle strength, prevention of functional decline and improvement in quality of life.[18] [113] Individuals with mobility limitations who engage in greater levels of total physical activity time compared with those who participate in more sedentary behaviors have better health outcomes.[114]

Common recommendations for patients with knee osteoarthritis are to stay moving. Dunlop et al. reported that lifestyle physical activity and exercise by self-report on the PASE scale was associated with improved function or maintenance of function over a 1 year period.[115] She also reported a 2-year longitudinal study looking at both

patients at risk for osteoarthritis and who already had osteoarthritis.[116] Those who participated in more light physical activity had significantly less disability and less disease progression over the 2-year period. Chmelo et al. provided consistent results in their study reporting those who had higher physical activity levels also performed better in functional tasks such as the 6-minute walk test and lower extremity strength.[117]

For older adults with chronic conditions, such as osteoarthritis, that present barriers to physical activity, the ACSM recommends participation to patient tolerance.[107] Even when guidelines are not met, increasing moderate to vigorous physical activity in physically inactive individuals with osteoarthritis is associated with reduced disability.[118] In a longitudinal study of patients with end stage knee osteoarthritis, moderate to vigorous physical activity was associated with increased symptoms of osteoarthritis, and incorporating lower volumes and/or intensity physical activity may be more appropriate.[119] Incorporating and encouraging individuals to participate in any level of physical activity may have greater public health implications, however more research is warranted to understand these relationships.

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Appendix B

IRB Approval Letter

TCApps

Plack, Leigh-ann <lap2191@tc.columbia.edu>

Exemption Notification - IRB ID: 18-433
1 message

Curt Naser <noreply@axiommentor.com> Wed, Jul 11, 2018 at 9:21 AM
Reply-To: Curt Naser <curtn@axiom-mentor.com>
To: lap2191@tc.columbia.edu

TEACHERS COLLEGE
COLUMBIA UNIVERSITY

Teachers College IRB *Exempt Study Approval*

To: Leigh-ann Plack
From: Paul Kran, Director
Subject: IRB Approval: 18-433 Protocol
Date: 07/11/2018

Thank you for submitting your study entitled, "*Physical Activity Behavior in Adults with Osteoarthritis*;" the IRB has determined that your study is **Exempt** from committee review (Category **4**) on 07/11/2018.

Please keep in mind that the IRB Committee must be contacted if there are any changes to your research protocol. The number assigned to your protocol is **18-433**. Feel free to contact the IRB Office by using the "Messages" option in the electronic Mentor IRB system if you have any questions about this protocol.

Please note that your Consent form bears an official IRB authorization stamp and is attached to this email. Copies of this form with the IRB stamp must be used for your research work. Further, all research recruitment materials must include the study's IRB-approved protocol number. You can retrieve a PDF copy of this approval letter from the Mentor site.

Best wishes for your research work.

Sincerely,

Paul Kran

Director

Kran@tc.columbia.edu

Appendix C

Osteoarthritis Initiative Protocol

The Osteoarthritis Initiative (OAI) is a publically and privately funded longitudinal multicenter study examining the onset and progression of knee osteoarthritis. The OAI consists of 4,796 community dwelling men and women between the ages of 45 and 79 years of all ethnic backgrounds and who were at risk for or had knee osteoarthritis at the time of enrollment (2004-2006). These individuals were recruited from clinical sites around the United States. Recruitment centers include Brown University in Pawtucket RI; University of Pittsburgh in Pittsburgh, PA; University of Maryland and Johns Hopkins in Baltimore Maryland (2 clinic sites); University of California San Francisco in San Francisco CA; and The Ohio State University in Columbus, OH. No treatments were performed as part of the OAI; however, participants were asked to report any treatment they were receiving during the bi-annual data collection clinic visits.

The OAI provides an archive of data and images for pain, physical function, patient global assessment, and joint imaging for researchers to begin to understand osteoarthritis disease progression. Details of the OAI study protocol and inclusion and exclusion criteria can be publically viewed at http://www.oai.epi-ucsf.org.[1] The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center at the University of California at San Francisco.

Funding for this project includes the National Institute of Health and private funding through pharmaceutical companies managed through the Foundation for the National Institute of Health.

Objectives of the OAI

The purpose of the OAI is to improve public health through the prevention or alleviation of pain and disability from OA.

The principal scientific objectives guiding the design of the OAI cohort study are:

- To develop an ethnically diverse cohort of women and men ages 45 to 79 suitable for studying the natural history of, and risk factors for, the onset and progression of knee osteoarthritis.
- To determine the validity of radiographic, magnetic resonance imaging, biochemical and genetic measurements as biomarkers and potential surrogate endpoints for knee OA.

Study Population

The OAI recruits' participants to achieve the stated objectives and includes a sub-cohort of participants with symptomatic knee osteoarthritis and another with asymptomatic knee osteoarthritis who are selected based on specific characteristics that increase their risk of developing symptomatic knee OA during the study. The OAI also includes a small

reference sample of participants without knee OA and without risk factors present in the incidence OA group.

Inclusion Criteria for the entire cohort

- Male or female
- Ages 45-79
- All ethnic groups are eligible for the study

Inclusion Criteria for the Progression Sub-cohort

Subjects are included in the progression sub-cohort if they have symptomatic tibiofemoral knee OA at baseline in at least one knee including:

- Frequent knee symptoms in the past 12 months defined as "pain, aching or stiffness in or around the knee on most days" for at least one month during the past 12 months;
- Radiographic tibiofemoral knee OA, defined as definite tibiofemoral osteophytes (OARSI atlas grades 1-3, equivalent to Kellgren and Lawrence (K-L) grade 2 on the fixed flexion radiograph.

OAI Exclusion Criteria (Directly from the OAI Protocol[1])

- "Rheumatoid Arthritis (RA) or inflammatory arthritis, defined as self-report of a physician diagnosis and ever use of any RA-specific prescription medications. Participants who report that a doctor has told them they have RA, SLE, psoriatic

arthritis, ankylosing spondylitis or another inflammatory arthritis are asked about use of specific medications that are used primarily for RA and other forms of inflammatory arthritis: e.g. gold, methotrexate, etanercept, infliximab, leflunamide, plaquenil, etc. If the person has ever used any of these medications, they are excluded. If the participant reports having RA or inflammatory arthritis but none of these medications have been used, they are asked about symptoms of RA and excluded if the responses are suggestive of RA. RA symptoms are assessed with the connective tissue disease screening questionnaire from the Nurses' Health Study, a questionnaire that has been shown to have high sensitivity and specificity for RA. In addition, participants are considered to have possible inflammatory arthritis and are excluded if their baseline fixed flexion knee radiograph shows severe joint space narrowing or bone on bone in both the medial and lateral compartments of either knee without the presence of a definite tibiofemoral osteophyte in that knee.

- Unlikely to demonstrate measurable loss of joint space during the study, defined as severe joint space narrowing (OARSI joint space narrowing grade 3 or bone-on-bone) in both knees on the baseline fixed flexion knee radiograph, or unilateral TKR and severe joint space narrowing in the other knee
- Bilateral total knee joint replacement or plans to have bilateral knee replacement in the next 3 years
- Unable to undergo a 3.0 Tesla MRI exam of the knee because of contraindications or inability to fit in the scanner or in the knee coil. Self-report weight limits at the Initial Eligibility Interview are used to reduce number of persons attending the

screening visit who fail to pass the MRI knee coil and bore size screens. Men over 285lbs and women over 250lbs will be excluded.

- Positive pregnancy test
- Unable to provide a blood sample for any reason, including having had a bilateral radical mastectomy, bilateral graft or shunt for kidney dialysis, etc. or refusal to provide a blood sample.
- Use of ambulatory aids other than a single straight cane - for more than 50% of the time in ambulation
- Co-morbid conditions that might interfere with the ability to participate in a 4-year study
- Unlikely to reside in the clinic area for at least 3 years
- Current participation in a double-blind randomized controlled trial
- Unwilling to sign informed consent"

Recruitment

Recruitment for the initial enrollment involved 4 stages:

1. Patients were reached through mailings, advertisements in local newspapers, presentations at civic centers, churches and community centers along with a website about knee pain and knee osteoarthritis to identify clinical populations with OA

2. Telephone interviews were completed to determine initial eligibility using items such as demographics, knee symptoms, screening risk factors and exclusion criteria
3. For those who qualified on the telephone evaluation, additional eligibility assessments were performed at the Screening Clinic Visit
4. For those who still qualified after the Screening Clinic Visit, an Enrollment Clinic Visit at which the majority of the baseline data were collected, and the MRI exams performed.

Patient Confidentiality

Participant confidentiality is maintained through a multi-tiered approach:

- Only participants who agree to participate and sign an IRB-approved consent form and HIPAA authorization have data included in the publicly accessible dataset
- Participants are identified by a study ID number and 4 letter check code at each clinic site. The clinical site in which the participant attends is the only site that has access to the key to match study ID and patient name and contact information.
- All participant data are maintained in locked file cabinets and on secure networks with password protection at each clinical site with only necessary access by researchers and staff.

Public Access Datasets

OAI OnLine is the publicly accessible website providing a limited dataset, containing most examination measurements and questionnaire data with direct identifiers removed. The unique ID number assigned to the participant during the screening is used in this database, however the 4-letter code is not utilized in this database due to the potential of unmasking identity. To access this dataset, researchers complete a registration process and agree to the terms of the data use agreements.

Accelerometry Group

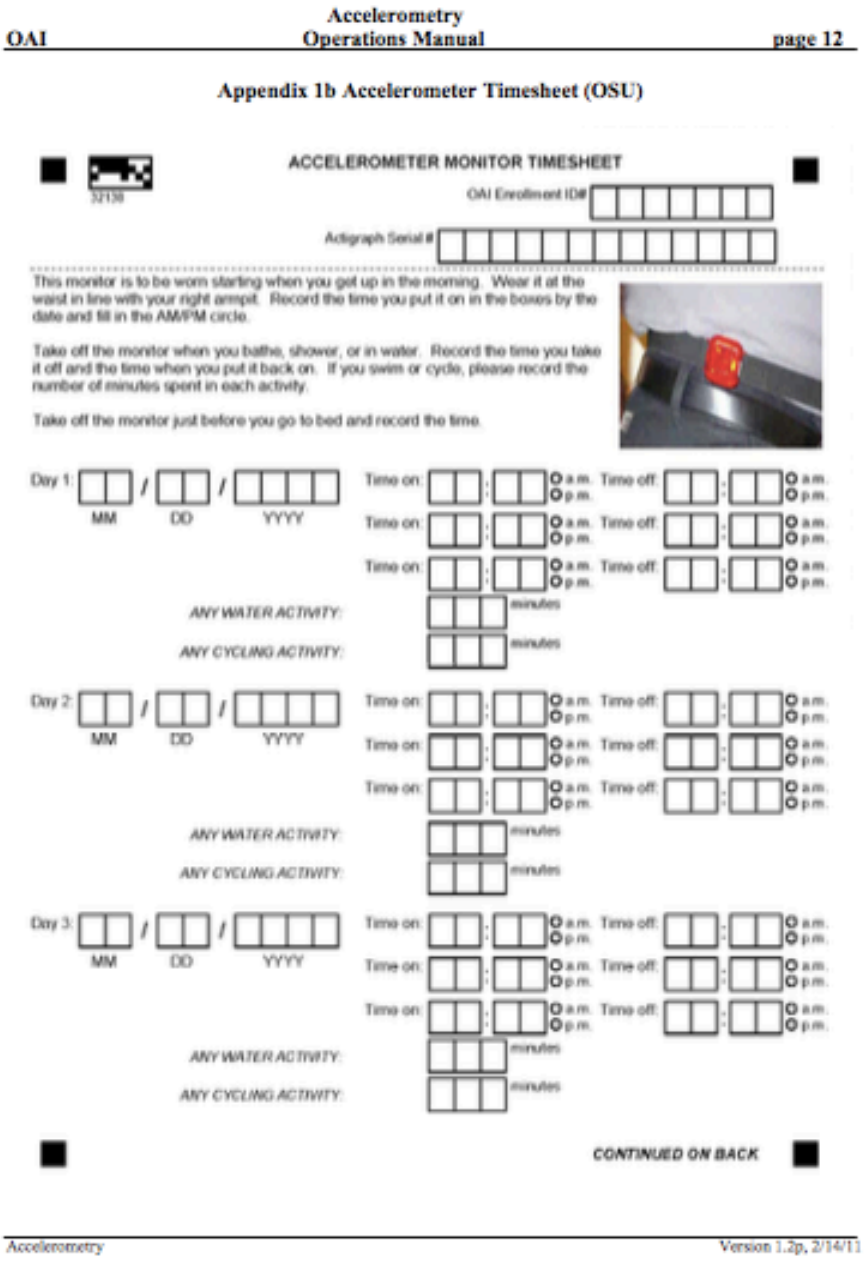
In a physical activity study, accelerometry data were collected on a subset of OAI participants with and without baseline radiographic OA in the incidence and progression groups, but not the reference sample, at the scheduled 48-month follow up examination. The purpose of this group is to measure physical activity in adults with osteoarthritis or at risk of osteoarthritis in as many participants as possible.

Eligibility required a scheduled OAI 48-month follow up visit between August 2008 and July 2010, with staggered starting months across the OAI sites. They did not have to be scheduled for the 72-month follow-up but had to be reliable to wear the accelerometers for 7 days and return it as soon as possible.

Participants were given a GTM-1 uniaxial Actigraph (Actigraph; Pensacola, Fl) attached to a belt and an accelerometer monitor timesheet (Figure 1-2) as well as a pre-

labeled package to return the device. Participants were fit and given instructions on wearing the accelerometer just above their right hip in line with their armpit in the same position each day. They were told to wear the accelerometer from waking to sleeping for 7 days straight except for showering; bathing or participating in any pool or water activities and to write down times the accelerometer was on and off daily on the monitor timesheets given to them. Upon completion of the 7 days, participants were instructed to use the pre-labeled box to return both the accelerometer with the belt and the timesheets for analysis.

Of the 4,796 participants, 1,543 OAI participants had visits that preceded the physical activity study start date and 541 were deceased, did not return at 48 months, or withdrew from the OAI study. Of the remaining 2,712 eligible participants, 2,127 consented to participate in accelerometer monitoring (78.4%). Of these 2,127 participants, 1,223 had radiographic knee OA at baseline. Accelerometry data were merged with OAI public data (from baseline to the 48-month examination) containing information on participant characteristics. [2]



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Appendix 1b Accelerometer Timesheet (OSU)

ACCELEROMETER MONITOR TIMESHEET

OAI Enrollment ID#

Actigraph Serial #

This monitor is to be worn starting when you get up in the morning. Wear it at the waist in line with your right armpit. Record the time you put it on in the boxes by the date and fill in the AM/PM circle.

Take off the monitor when you bathe, shower, or in water. Record the time you take it off and the time when you put it back on. If you swim or cycle, please record the number of minutes spent in each activity.

Take off the monitor just before you go to bed and record the time.

Day 1: MM / DD / YYYY — Time on: ; a.m. p.m. — Time off: ; a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

Day 2: MM / DD / YYYY — Time on: ; a.m. p.m. — Time off: ; a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

Day 3: MM / DD / YYYY — Time on: ; a.m. p.m. — Time off: ; a.m. p.m.

ANY WATER ACTIVITY: minutes

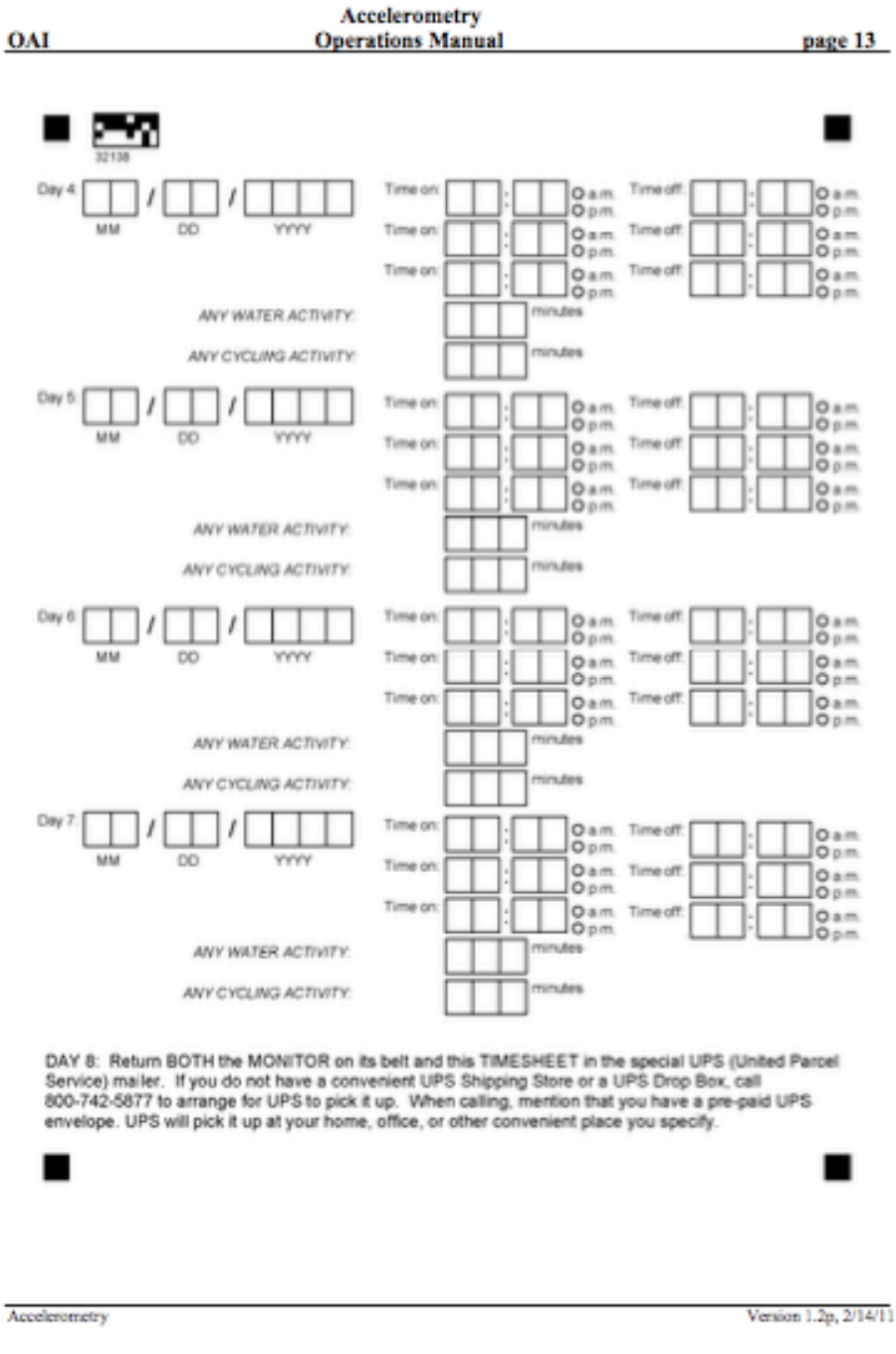
ANY CYCLING ACTIVITY: minutes

CONTINUED ON BACK

Accelerometry Version 1.2p, 2/14/11

Figure 4.

Accelerometer Monitor timesheet page 1 From OAI Operations Manual



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Day 4: MM / DD / YYYY — Time on: : a.m. p.m. — Time off: : a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

Day 5: MM / DD / YYYY — Time on: : a.m. p.m. — Time off: : a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

Day 6: MM / DD / YYYY — Time on: : a.m. p.m. — Time off: : a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

Day 7: MM / DD / YYYY — Time on: : a.m. p.m. — Time off: : a.m. p.m.

ANY WATER ACTIVITY: minutes

ANY CYCLING ACTIVITY: minutes

DAY 8: Return BOTH the MONITOR on its belt and this TIMESHEET in the special UPS (United Parcel Service) mailer. If you do not have a convenient UPS Shipping Store or a UPS Drop Box, call 800-742-5877 to arrange for UPS to pick it up. When calling, mention that you have a pre-paid UPS envelope. UPS will pick it up at your home, office, or other convenient place you specify.

Accelerometry Version 1.2p, 2/14/11

Figure 5.

Accelerometer Monitor Timesheet page 2 from OAI Operations Manual

References

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Appendix D

Osteoarthritis Initiative Survey Documents

Accelerometry

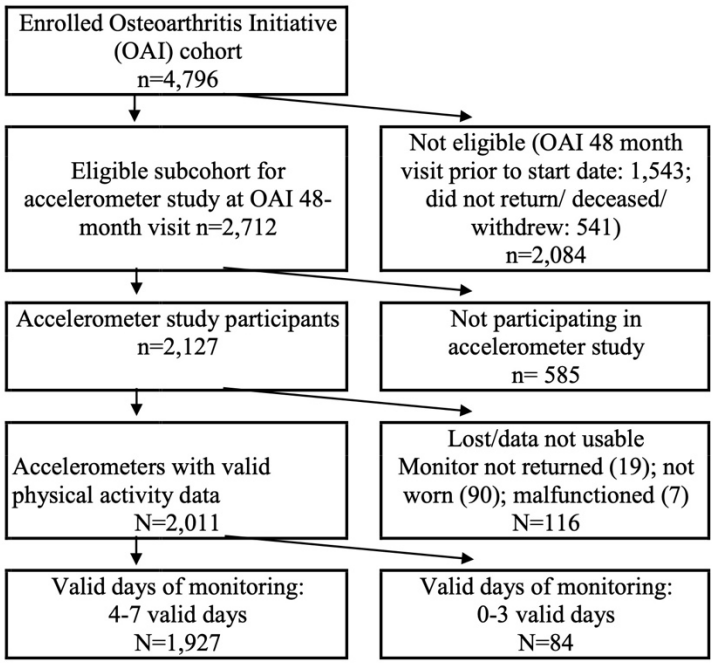
SAS Dataset Name: Accelerometry

General description:
An Osteoarthritis Initiative (OAI) physical activity ancillary study (Dr. Dorothy Dunlop, AS05-10) collected accelerometer data on a subgroup of OAI participants. Physical activity was monitored using ActiGraph GT1M uniaxial accelerometers (ActiGraph; Pensacola, FL). As shown in Figure 1 below, a subset of 2,712 OAI participants were invited to join this ancillary study. The number of OAI participants who consented to participate was 2,712. Of these 2,011 adults returned their monitor with activity data. A valid day of accelerometer monitoring data was determined from recording evidence the monitor was worn at least 10 hours/day. A total of 1,927 participants had 4-7 valid days of monitoring, which is sufficient to estimate typical physical activity (1).

The accelerometry dataset contains for each person the average over the valid monitoring days of each physical activity measure and provides variables that indicate whether or not physical activity guidelines were attained during the week of monitoring.

The detailed minute-by-minute and day-by-day accelerometry data are in separate accelerometry datasets (AccelDataXX_SAS.zip, where XX denotes the visit), and can be downloaded from the clinical data section of the OAI Online website:
https://www.oai.ucsf.edu/datarelease/DataClinical.asp#Datasets.

Figure 1. Flow chart of OAI participants in OAI 48-month accelerometer study



Accelerometer monitoring in the OAI:
Eligibility for accelerometer monitoring required a scheduled OAI 48-month follow-up visit between August 2008 and July 2010, with staggered starting months across the OAI sites. A total of 2,127 persons consented to participate in accelerometer monitoring representing 78.4% of eligible participants (2,712). Another 1,543 OAI participants had visits that preceded the accelerometer study start date and 541 were deceased/did not return at 48 months/ withdrew from OAI study. Physical activity was objectively measured using a GT1M ActiGraph accelerometer. Trained OAI research staff gave uniform scripted in-person instructions. Each participant was told to wear the accelerometer on a belt at the natural waistline on the right hip in line with the right axilla upon arising in the morning and continuously until retiring at night, except during water activities, for seven consecutive days. Participants maintained a daily log to record time spent in water and cycling activities, which may not be fully captured by accelerometers. Daily log data (not electronically archived) indicated that participants spent in little time in water and cycling activities (median 0 minutes/day, interquartile range = 0.0 to 3.4 minutes/day); this information indicates little activity was missed or underestimated by accelerometer monitoring. Participants returned the accelerometers to the research center; where data were downloaded using the manufacturer's software, and checked for valid data recording.

A total of 2,001 adults provided one or more valid days of accelerometer monitoring data. A valid data of accelerometer monitoring was based on recording evidence that the monitor was worn at least 10 hours.

Accelerometers used in the OAI:
Unlike pedometers, which measure steps, but give no information about the intensity of those steps, accelerometers constantly sample activity for accelerations, and are therefore able to provide information on all three dimensions of physical activity (frequency, intensity, and duration). Physical activity in this OAI sample was monitored in all study participants using a GT1M ActiGraph uniaxial accelerometer. The GT1M ActiGraph is a small uniaxial accelerometer that measures vertical acceleration and deceleration (2). The accelerometer acceleration signal is filtered and digitized by an 8-bit analog-digital (A-D) converter at 30 samples per second. The A-D converter measures the magnitudes of the captured accelerations.

The output from an accelerometer is an ***activity count*** (explained below). Spurious accelerometer counts were identified by negative counts (<1/1,000,000 recorded negative activity counts); these spurious values were set to missing on a minute by minute basis. Accelerometer accuracy (walking speed(3)) and test-retest reliability(4) of under field conditions have been established in many populations including persons with OA (3-7). Uniaxial accelerometer validation studies against "gold standard" whole-body indirect calorimetry showed high correlation with metabolic equivalent (r=0.93) and total energy expenditure (r=0.93) (8).

What is an activity count?:
An activity count is the weighted sum of the number of vertical movements measured over a time period (e.g. in this case 1 minute), where the weights are proportional to the magnitude of ***measured*** acceleration or deceleration. In contrast to pedometers, an accelerometer measures acceleration and changes in acceleration. Gravity's acceleration is called Gs. For example, when you accelerate your car, the Gs push you back into the seat and vice versa when you hit the brakes (the harder you hit pedals the more noticeable the Gs). Conceptually, accelerometer

counts increase with the increased forces. As you walk, you go up a little and then you come back down, running makes this vertical 'up and down' movement more noticeable. As your movement becomes more noticeable, the counts increase. It is precisely this capability that enables accelerometers to provide data on all three dimensions of physical activity: frequency, duration, and intensity, since data is collected in 'real time'.

Identifying valid days of accelerometer monitoring:
An important analytical step is the translation of accelerometer counts into physical activity measurements. We used methodology validated in adults with osteoarthritis (9). A basic building block in this process is the assessment and interpretation of 'nonwear time'. Nonwear relates to periods when activity counts register as '0', because the accelerometer is not being worn. The challenge is to distinguish '0' due to no activity from '0' due to the monitor not being worn and lying on a table. Analytically, non-wear periods were defined as ≥90 consecutive minutes with zero activity counts (allowing for interruptions of up to 2 consecutive minutes with counts<100)(10). A valid day of accelerometer monitoring was defined as 10 or more wear hours in a 24-hour period (1). Note that the 10 hours of wear time was not required to be continuous.

Accelerometer cutpoints to assess physical activity intensity:
Accelerometer 'cutpoints' are thresholds assigned by researchers to divide activity counts into physical activity intensity levels (e.g., light, moderate, and vigorous). The intensity of physical activity is defined in terms of energy expenditure measured in metabolic equivalent task (MET) units. Cut points are estimated to identify activity counts that corresponds to designated energy expenditure values (e.g., light 1.5 to <3 METS, moderate 3 to <6 METS, vigorous ≥6 METS).

Table 2. Accelerometer cut points for Metabolic Equivalent of Task (MET) energy expenditure values

	Activity Count/Minute Cut Points		
Gross MET Value/Intensity	Troiano(1)	Freedson(11)	Swartz(12)
1.5 to<3 METs (light)	100- 2019	100-1951	100-573
3 to 6 METs (moderate)	2020-5998	1952- 5724	574-4944
≥6 METs (vigorous or greater)	5999+	5725 +	4945+

There are many established/validated cutpoints. We applied cutpoints most commonly cited in the literature, which are shown in Table 2. A benchmark set of cutpoints are those published by Troiano,(1) which were applied to the general adult population from the National Health and Nutrition Examination Study (NHANES). We also provide physical activity outcomes based on other cutpoints due to their importance from earlier publications, which includes Freedson (11) cutpoints for the general adult population and Swartz (12) cutpoints for older adult populations. What distinguishes these thresholds is the age of the participants tested and the physical activity engaged in to arrive at the regression equation that established the cutpoints, e.g. treadmill vs. community activity. The data released for OAI participants have been processed applying the cutpoints published by Swartz (12), Freedson (11), and Troiano (1) to each minute of accelerometer output.

The effect of cutpoint choices can best be demonstrated by graphically applying the values to identical accelerometer output, as shown in Figures 2-4 below. Cutpoints appear as horizontal lines drawn through the data. Notice how activity occurring at identical count levels can be

deemed either 'light' (counts occurring above the green line but under the brown line) or 'moderate' (counts occurring above the brown line but under the red line) intensity, depending on the cutpoints utilized. Deciding a priori which cutpoints to use in data analysis is a critical decision and will affect your findings. It is therefore important to include a data cutpoint citation in reporting accelerometer data, and a justification for its use in the population of interest.

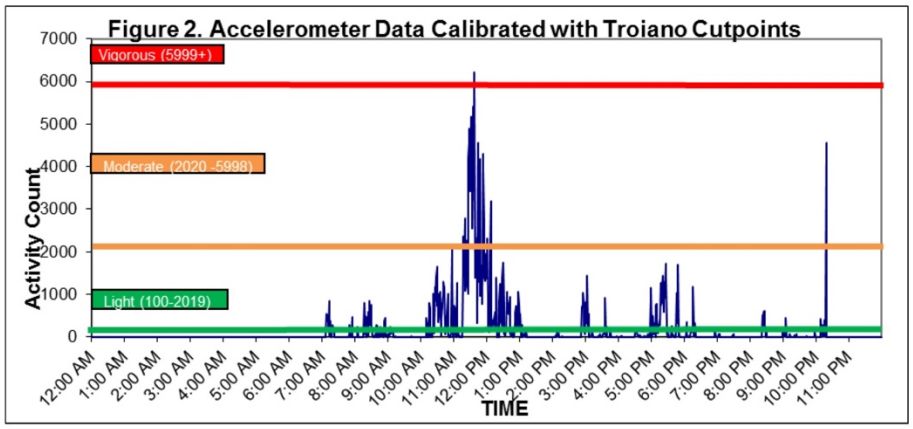


Figure 2. Accelerometer Data Calibrated with Troiano Cutpoints
Vigorous (5999+)
Moderate (2020 -5998)
Light (100-2019)
Activity Count
TIME

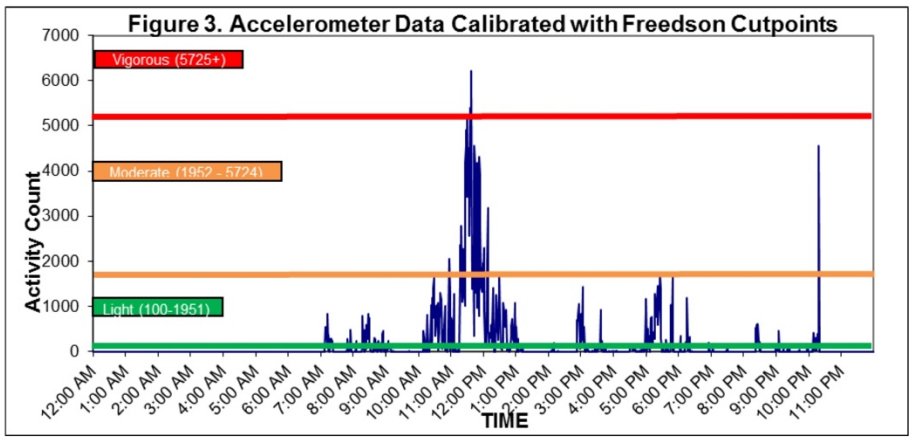


Figure 3. Accelerometer Data Calibrated with Freedson Cutpoints
Vigorous (5725+)
Moderate (1952 - 5724)
Light (100-1951)
Activity Count
TIME

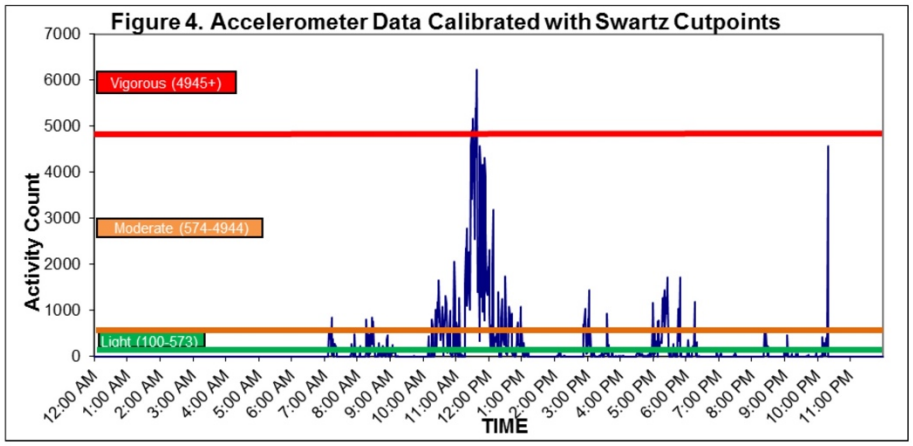


Figure 4. Accelerometer Data Calibrated with Swartz Cutpoints
Vigorous (4945+)
Moderate (574-4944)
Light (100-573)
Activity Count
TIME

Physical activity guidelines:
Physical activity guidelines have been periodically updated since the initial 1995 CDC-ACSM Guidelines (Centers for Disease Control-American College of Sports Medicine) were published in JAMA by Pate et al (13). In 1996 the Surgeon General Guidelines were published (14). In 2003, a committee was convened to update the guidelines, with additional input from the American Heart Association. The final recommendations from the 2003 committee were published in 2007(15). However, the 2008 Physical Activity Guidelines for Americans, is the first official US government policy on physical activity recommendations for optimal health, issued by the U.S. Department of Health and Human Services (DHHS), written by the Physical Activity Guidelines Advisory Committee (PAGAC), based on the scientific report assembled by an independent Federally Appointed Committee of Advisors. The full set of recommendations can be viewed at http://www.health.gov/paguidelines/guidelines/default.aspx#toc. Highlights pertaining to this data release are given in Table 3.

Table 3. Summary of Physical Activity Guidelines 2003-2008

Population Group	**Aerobic Guidelines**		**Strength Training Guidelines***
	Moderate Intensity Activity	Vigorous Intensity Activity	
General Adults (ACSM, 2003)	30 moderate bout** minutes on each of 5 days/week	20 vigorous bout** minutes on each of 3 days/week	2 or more days/week, all muscle groups
General Adults (DHHS, 2008)	150 moderate bout **minutes spread across the week	75 vigorous bout** minutes spread across the week	2 or more days /week, all muscle groups
Adults with Arthritis (DHHS, 2008)	150 moderate-to-vigorous bout** minutes spread across the week***		2 or more days /week, all muscle groups

*The OAI did not collect data to assess attainment of strength training guidelines.
**Minutes are accumulated in 10 minute bouts
***Activities are recommended to be low impact, not painful, and low risk of joint injury.

Aerobic guideline attainment programming decisions:
The attainment of the aerobic guidelines was based on a typical week of physical activity. However, for some participants the number available of valid monitoring days was less than seven days. In those cases, we followed the literature which supports four days as a standard minimum monitoring time needed to capture typical physical activity patterns. Our approach is consistent with the methodology applied to the NHANES data to assess guideline attainment (1). This process is summarized in Table 4.

Table 4. Assessed Guideline Attainment Based on Available Valid Monitoring Days	
Aerobic Guideline	Number of valid days
General Adults (ACSM, 2003)	• For persons with 7 valid days of data (n= 1511, 75.5%) guideline attainment was determined according to tabled outline. • For persons with 4-6 valid days of data (n=317, 20.8%), we estimated the probability that they would attain guidelines by the end of 7 days, using NHANES methodology.(1) • For persons with 0-3 valid days of data, (N=73, 3.7%), no guideline attainment was assessed.
General Adults (DHHS, 2008) Adults with Arthritis (DHHS, 2008)	• For persons with 7 valid days of data (n= 1511, 75.5%) guideline attainment was determined according to tabled outline. • For persons with 4-6 valid days of data (n= 317, 20.8%), we used the average daily physical activity experience to estimate 7 days of activity for the purposes of determining guideline attainment(16) • For persons with 0-3 valid days of data, (n= 73, 3.7%), no guideline attainment was assessed.

Data Structure/Contents:
These datasets contain one record per participant. Each participant included had 4-7 valid days of accelerometer monitoring, i.e. with 10+ wearing hours. The variable uniquely identifying a record is ID, and the datasets are sorted by ID, which can be used to merge/join to data in other datasets.

A full list and description of all the variables contained in these datasets can be found in the contents.pdf.

The 72-month accelerometry data was released in 2016.

Condition of data:
- **Known data errors:** None at this time. Systematically inspected, cleaned, processed.
- **Dataset strengths/weaknesses:** None at this time.

General strategies for use:
When using with other datasets, merge/join by ID.

Analysts are encouraged to always output and view SAS variable labels in their entirety to ensure important information about the variables is not lost. The maximum SAS label length is 160 characters.

References:

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11. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Medicine & Science in Sports & Exercise. 1998;30(5):777-81.
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Prevention and the American College of Sports Medicine. Journal of the American Medical Association. 1995;273(5):402-7.
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Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month ~~VISIT~~	ID	~~ACROS~~

HEALTH HISTORY AND MEDICAL CONDITIONS

16. Have you ever had a heart attack? **HRTAT** **COMORB**

1 O Yes 0 O No .D O Don't know

17. Have you ever been treated for heart failure? (You may have been short of breath and the doctor may have told you that you had fluid in your lungs or that your heart was not pumping well.)

1 O Yes 0 O No .D O Don't know **HRTFAIL**

18. Have you had an operation to unclog or bypass the arteries in your legs? **BYPLEG**

1 O Yes 0 O No .D O Don't know

19. Have you had a stroke, cerebrovascular accident, blood clot or bleeding in the brain, or transient ischemic attack (TIA)? **STROKE**

1 O Yes 0 O No .D O Don't know

Go to Question #21.

a. Do you have difficulty moving an arm or leg as a result of the stroke or cerebrovascular accident? ~~STRDIF~~

O Yes O No O Don't know

20. Do you have asthma? **ASTHMA**

1 O Yes 0 O No .D O Don't know

Go to Page 9, Question #22.

a. Do you take medicines for your asthma? **ASTMEDS**

1 O Yes 0 O No .D O Don't know

(i.) When do you usually take medicine for your asthma? **Please mark only one answer.** **AMWHEN**

1 O Only with flare-ups of my asthma

2 O Regularly, even when I'm not having a flare-up

Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month	ID	ACROS

VISIT

HEALTH HISTORY AND MEDICAL CONDITIONS

21. Do you have emphysema, chronic bronchitis, or chronic obstructive lung disease (also called COPD)? **LUNG**

1O Yes 0O No .DO Don't know

Go to Question #22.

a. Do you take medicines for your lung disease? **LGMEDS**

1O Yes 0O No .DO Don't know

(i.) When do you usually take medicine for your lung disease? **LMWHEN**
Please mark only one answer.

1O Only with flare-ups of my emphysema, bronchitis or COPD

2O Regularly, even when I'm not having a flare-up

22. Do you have stomach ulcers, or peptic ulcer disease? **ULCER**

1O Yes 0O No .DO Don't know

Go to Question #23.

a. Has this condition been diagnosed by endoscopy (where a doctor looks into your stomach through a scope) or an upper GI or barium swallow study (where you swallow chalky dye and then x-rays are taken)? **ULCERDX**

1O Yes 0O No .DO Don't know

23. Do you have diabetes (high blood sugar)? **DIAB**

1O Yes 0O No .DO Don't know

Go to Page 10, Question #24.

a. How has your diabetes been treated? **Please mark all that apply.**

1O Modifying my diet **DIABTX1**
1O Medications taken by mouth **DIABTX2**
1O Insulin injections **DIABTX3**
1O Not treated / watchful waiting **DIABTX4**

b. Has the diabetes caused any of the following problems? **Please mark all that apply.**

1O Problems with your kidneys **DIABPR1**
1O Problems with your eyes, treated by an ophthalmologist (medical eye doctor) **DIABPR2**
1O Has not caused problems **DIABPR3**

Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month ~~VISIT~~	ID	~~ACROS~~

HEALTH HISTORY AND MEDICAL CONDITIONS

24. Have you ever had any of the following problems with your kidneys?

a. Poor kidney function (blood tests showed high creatinine)? **KIDFXN**
1 O Yes **0** O No **.D** O Don't know

b. Have used hemodialysis or peritoneal dialysis? ~~HEMOD~~
O Yes O No O Don't know

c. Have received a kidney transplant? **KIDTRAN**
1 O Yes **0** O No **.D** O Don't know

25. Do you have rheumatoid arthritis? **RA**

1 O Yes **0** O No **.D** O Don't know

Go to Question #26.

a. Do you take medicines for your rheumatoid arthritis regularly? **RAMEDS**
1 O Yes **0** O No **.D** O Don't know

26. Do you have lupus (systemic lupus erythematosus)? ~~LUPUS~~
O Yes O No O Don't know

27. Do you have polymyalgia rheumatica? **POLYRH**
1 O Yes **0** O No **.D** O Don't know

VISIT

Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month	ID	ACROS

COPING STRATEGIES

Individuals who experience pain have developed a number of ways to cope, or deal with, their pain. Below is a list of things that people have reported doing when they feel pain. For each activity, please indicate, using the scale below, how much you engage in that activity when you feel pain, where a 0 indicates you never do that when you are experiencing pain, a 3 indicates you sometimes do that when you are experiencing pain, and a 6 indicates you always do it when you are experiencing pain. Please point to any number on this scale.
(Examiner Note: REQUIRED. Show Card 24a.)

0 1 2 3 4 5 6

Never do — Sometimes do — Always do

62a. When I feel pain...	0	1	2	3	4	5	6	Don't know	Refused
CSQDVAT	0	1	2	3	4	5	6	.D	.R
a. I think of things I enjoy doing. COPE1	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQRPS **b.** I just think of it as some other sensation, such as numbness. COPE2	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQCAT **c.** It is terrible and I feel it is never going to get any better. COPE3	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQIGSN **d.** I don't pay any attention to it. COPE4	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQPRHP **e.** I pray for the pain to stop. COPE5	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQCSS **f.** I tell myself I can't let the pain stand in the way of what I have to do. COPE6	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQIBA **g.** I do something active, like household chores or projects. COPE7	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQDVAT **h.** I replay in my mind pleasant experiences in the past. COPE8	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQRPS **i.** I pretend it is not a part of me. COPE9	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQCAT **j.** I feel I can't stand it anymore. COPE10	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQIGSN **k.** I ignore it. COPE11	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQPRHP **l.** I try to think years ahead, what everything will be like after I've gotten rid of the pain. COPE12	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQCSS **m.** I see it as a challenge and don't let it bother me. COPE13	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref
CSQIBA **n.** I do something I enjoy, such as watching TV or listening to music. COPE14	O 0	O 1	O 2	O 3	O 4	O 5	O 6	O DK	O Ref

Coping Strategies Questionnaire (CSP), Two-item version.

Scoring for WOMAC© Likert 3.1

The WOMAC© Likert 3.1 was a priority instrument for the study as indicated by a star next to each question in the Follow-up Visit Workbook.

Please go to: http://www.womac.org for more information about the WOMAC© Likert 3.1.

WOMAC© subscales

There are three WOMAC© subscales: pain, stiffness and disability. The time period covered by the subscales is the "last 7 days". Subscale scores are the sum of individual item scores for all items in the subscale.

Knee pain

The individual items in the pain subscale are:

Activity	Variable (right knee)	Variable (left knee)
Walking	**WPRKN1**	**WPLKN1**
Stairs	**WPRKN2**	**WPLKN2**
In bed	**WPRKN3**	**WPLKN3**
Sit or lie down	**WPRKN4**	**WPLKN4**
Standing	**WPRKN5**	**WPLKN5**

Each knee pain item is scored on a 5-point scale:
0 = None
1 = Mild
2 = Moderate
3 = Severe
4 = Extreme
.D = Don't know
.R = Refused
.X = Don't do*

*The following variables have the .X (don't do) scoring option: WPRKN2, WPLKN2.

The pain subscale scores are calculated for the right and left knee separately. The pain subscale possible score range is 0-20.

Score	Variable (right knee)	Variable (left knee)
Pain subscale scores	**WOMKPR**	**WOMKPL**

Please note that pain data was collected and pain scores were calculated for participants who had replaced knees. Please refer to the Outcomes dataset on OAI Online for knee replacement outcomes data.

(Note: Pages 11Q, 13Q, 15Q, 16Q, 17Q, 19Q, 21Q, and 22Q of the OAI Follow-up Visit Workbook are not being displayed.)

Knee stiffness
The individual items in the stiffness subscale are:

Activity	Variable (right knee)	Variable (left knee)
In morning	**WSRKN1**	**WSLKN1**
Later in day	**WSRKN2**	**WSLKN2**

Each knee stiffness item is scored with the same scale used for knee pain, except the .X scoring option (see previous page) is not available.

The stiffness subscale scores are calculated for the right and left knee separately. The stiffness subscale possible score range is 0-8.

Score	Variable (right knee)	Variable (left knee)
Stiffness subscale scores	**WOMSTFR**	**WOMSTFL**

Disability
The individual items in the disability subscale are:

Activity	Variable (right knee)	Variable (left knee)
Down stairs	**DIRKN1**	**DILKN1**
Up stairs	**DIRKN2**	**DILKN2**
Stand from sitting	**DIRKN3**	**DILKN3**
Standing	**DIRKN4**	**DILKN4**
Bending	**DIRKN5**	**DILKN5**
Walking	**DIRKN6**	**DILKN6**
In car/out of car	**DIRKN7**	**DILKN7**
Shopping	**DIRKN8**	**DILKN8**
Socks on	**DIRKN9**	**DILKN9**
Get out of bed	**DIRKN10**	**DILKN10**
Socks off	**DIRKN11**	**DILKN11**
Lying down	**DIRKN12**	**DILKN12**
Get in/out of bathtub	**DIRKN13**	**DILKN13**
Sitting	**DIRKN14**	**DILKN14**
On/off toilet	**DIRKN15**	**DILKN15**
Heavy chores	**DIRKN16**	**DILKN16**
Light chores	**DIRKN17**	**DILKN17**

Each disability item is scored for difficulty with the same scale used for pain and stiffness (see previous page).

*The following variables have the .X (don't do) scoring option: DIRKN1, DILKN1, DIRKN2, DILKN2, DIRKN5, DILKN5, DIRKN8, DILKN8, DIRKN13, DILKN13, DIRKN16, DILKN16, DIRKN17 and DILKN17.

The disability subscale scores are calculated for the right and left knee separately. The disability subscale possible score range is 0-68.

Score	Variable (right knee)	Variable (left knee)
Disability subscale scores	**WOMADLR**	**WOMADLL**

(Note: Pages 11Q, 13Q, 15Q, 16Q, 17Q, 19Q, 21Q, and 22Q of the OAI Follow-up Visit Workbook are not being displayed.)

Total scores

The total scores are the sum of the pain, stiffness and disability subscale scores for the right and left knee, respectively. The possible score range is 0-96.

Score	Variable (right knee)	Variable (left knee)
Total scores	WOMTSR	WOMTSL

Score calculations
An individual response of:

.D = Don't know
.R = Refused
.X = Don't do

for any item is treated as missing data. If there are more missing values than the specified cut-off (see below), the calculated score is missing and set to a special missing value.

Pain subscale score: If 1 of the 5 items is missing, it is replaced by the average score of the other 4 items. If 2 or more items are missing, the pain score is missing for that knee.

Stiffness subscale score: If 1 of the 2 items is missing, it is replaced by the non-missing score. If both items are missing, the stiffness score is missing for that knee.

Disability subscale score: If 1, 2 or 3 of the 17 items are missing, they are replaced by the average of the non-missing scores. If 4 or more items are missing, the disability score is missing for that knee.

Total score: If any of the 3 subscale scores are missing, the total score is missing for that knee.

(Note: Pages 11Q, 13Q, 15Q, 16Q, 17Q, 19Q, 21Q, and 22Q of the OAI Follow-up Visit Workbook are not being displayed.)

Type of Follow-up Visit	OAI Participant ID #	Acrostic
○ 12-month ○ 24-month ○ 36-month ○ 48-month ○ Interim 6-month VISIT	ID	ACROS

HEALTH SURVEY

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

For each of the following questions, please fill in the bubble that best describes your answer. If you are unsure about how to answer a question, please give the ONE best answer you can.

9. In general, would you say your health is...?

HSPSS

1 ○ Excellent 2 ○ Very good 3 ○ Good 4 ○ Fair 5 ○ Poor SF1

HSMSS

10. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf SF2	1 ○	2 ○	3 ○
b. Climbing several flights of stairs SF3	1 ○	2 ○	3 ○

11. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like SF4	1 ○	2 ○	3 ○	4 ○	5 ○
b. Were limited in the kind of work or other activities SF5	1 ○	2 ○	3 ○	4 ○	5 ○

Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month VISIT	ID	ACROS

HEALTH SURVEY

12. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Accomplished less than you would like **SF6**	1 O	2 O	3 O	4 O	5 O
b. Didn't do work or activities as carefully as usual **SF7**	1 O	2 O	3 O	4 O	5 O

13. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? **SF8**

1 O Not at all 2 O A little bit 3 O Moderately 4 O Quite a bit 5 O Extremely

14. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks . . .

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful? **SF9**	1 O	2 O	3 O	4 O	5 O
b. Did you have a lot of energy? **SF10**	1 O	2 O	3 O	4 O	5 O
c. Have you felt downhearted and depressed? **SF11**	1 O	2 O	3 O	4 O	5 O

15. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)? **SF12**

1 O All of the time 2 O Most of the time 3 O Some of the time 4 O A little of the time 5 O None of the time

Type of Follow-up Visit	OAI Participant ID #	Acrostic
O 12-month O 24-month O 36-month O 48-month O Interim 6-month	ID	ACROS

VISIT

FRACTURE HISTORY

29. Since we last spoke to you about 12 months ago, have you been told by a doctor that you broke or fractured a bone(s)?

1 O Yes 0 O No .D O Don't know BONFX

0 → Go to Question #30.

a. What bone(s) did the doctor say that you broke or fractured?
Please mark all that apply.

1 O Hand **BONFX1**
1 O Lower arm or wrist **BONFX2**
O Elbow BONFX3
O Upper arm (humerous) BONFX4
1 O Shoulder, clavicle, and/or scapula **BONFX5**
1 O Spine or back (vertebra) **BONFX6**
O Tailbone (sacrum and/or coccyx) BONFX7
O Pelvis BONFX8
O Hip BONFX9
O Upper leg (not hip) BONFX10
O Knee (patella) BONFX11
1 O Lower leg or ankle **BONFX12**
1 O Foot (not toe) **BONFX13**
O Other BONFX15 ***(Please specify:)***
.D O Don't know / Don't remember **BONFX14**

BONFXOH
BONFXHP
HPFXFU
BONFX16

30. During the past 12 months, have you fallen and landed on the floor or ground?

1 O Yes 0 O No .D O Don't know FALL

0 → Go to Page 13, Question #31.

a. How many times have you fallen in the past 12 months?
If you are unsure, please make your best guess.

0 *(None)*
1 O One
2 O Two or three
3 O Four or five FALLNUM
4 O Six or more
.D O Don't know
.R *(Refused)*

FALLCV

Type of Follow-up Visit	OAI Participant ID #	Acrostic	Staff ID#
O 12-month O 18-month O 24-month O 30-month O 36-month O 48-month	ID	ACROS	STFID8

VISIT

Page ☐ of ☐ PAGE PAGES

MEDICATION INVENTORY FORM

★ **159.** Did the participant bring in or identify ALL prescription medications that they took during the past 30 days?

1 O All **2** O Some **0** O No **3** O Took none **RX30**

(a.) Total number recorded: ☐☐ **RX30NUM** medications

Arrange for telephone call to complete MIF

Record the name of the prescription medicine, duration of use, formulation code, whether the participant is still using the medication, and frequency of use.
(Examiner Note: REQUIRED. Show Card #36.) **MIFNAME** **INGNAME** **INGCODE**

1. Name:

MIFDUR **Duration of use:** **1** O < 1 month **2** O 1 month - 1 year **3** O 1 - 3 years **4** O 3 - 5 years **5** O > 5 years **.D** O Don't know

FRMCODE **Formulation code:** ☐☐

MIFUSE **Still using?** **1** O Yes **0** O No

MIFFREQ **Frequency?** **1** O As needed **2** O Regular

RXACTM	RXCLCTN	RXIHYAL	RXNTRAT	RXSALIC
RXANALG	RXCLCXB	RXISTRD	RXOSTRD	RXSAME
RXASPRN	RXCOX2	RXMSM	RXOTHAN	RXTPRTD
RXBISPH	RXFLUOR	RXNARC	RXRALOX	RXVIT_D
RXCHOND	RXGLCSM	RXNSAID	RXRFCXB	RXVLCXB

Formulation Codes:
1=oral tablet or capsule; 2=oral liquid; 3=topical liquid, lotion, or ointment; 4=ophthalmic; 5=rectal or vaginal; 6=inhaled; 7=injected; 8=transdermal patch; 9=powder; 10=nasal

PASE© Scoring

The Physical Activity Scale for the Elderly (PASE©) is a registered trademark, PASE© 1991 New England Research Institutes, Inc. This copyrighted instrument may not be displayed. Therefore pages 35Q-39Q of the OAI Follow-up Visit Workbook are not being displayed.

Please go to:

http://www.neriscience.com/web/MultiPiecePage.asp_Q_PageID_E_71_A_PageName_E_instrumentsforsale#88

for more information about the PASE©.

PASE© domains

The PASE© covers 3 domains of activity: leisure activities, household activities and occupational activities. The time period covered by PASE© is the "past 7 days".

Leisure activities

The individual leisure activity items are:

Activity	Variable (days/week)	Variable (hours/day)
Sitting	**PASE1**	**PASE1HR**
Walking	**PASE2**	**PASE2HR**
Light sport/recreation	**PASE3**	**PASE3HR**
Moderate sport/recreation	**PASE4**	**PASE4HR**
Strenuous sport/recreation	**PASE5**	**PASE5HR**
Muscle strength/endurance	**PASE6**	**PASE6HR**

Each activity is scored for frequency using a 4-point scale:
0 = Never
1 = Seldom (1-2 days)
2 = Sometimes (3-4 days)
3 = Often (5-7 days)
.D = Don't know
.R = Refused

and for hours per day using a 4-point scale:
1 = <1
2 = 1 to <2
3 = 2 to 4
4 = >4
.D = Don't know

Household activities

The individual household activity items are:

Activity	Variable
Light housework	**HOUACT1**
Heavy housework	**HOUACT2**
Home repairs	**HOUACT3**

(Note: Pages 35Q-39Q of the Follow-up Visit Workbook are not being displayed.)

Lawn work/yard care	**HOUACT4**
Outdoor gardening	**HOUACT5**
Caring for another person	**HOUACT6**

Each household activity item is scored:
0 = No
1 = Yes
.D = Don't know
.R = Refused

Occupational activities

The individual occupational items are:

Item	Variable
Work (pay/volunteer)	**WORK7**

The work (pay/volunteer) item is scored:
0 = No
1 = Yes
.D = Don't know
.R = Refused

Item	Variable
Number of hours worked	**WKHR7CV**

WORK7, WORKHR7 (number of hours worked) and WORK1HR (less than 1 hour worked/don't know) are collapsed into WKHR7CV, a continuous variable. WORKHR7 and WORK1HR are unreleased. If WORK1HR is answered less than 1 hour worked, WKHR7CV is calculated as 1 hour worked.

Item	Variable
Occupational activity level	**WORKAMT**

The activity level item is scored on a 4-point scale:
1 = Sitting
2 = Sitting/standing/walking
3 = Walking/handling <50 lbs
4 = Walking/handling >50 lbs
.D = Don't know

Total score

12 items are weighted depending on the strenuousness of the activity, and then summed to give the PASE© total score.

Score	Variable
Total score	**PASE**

(Note: Pages 35Q-39Q of the Follow-up Visit Workbook are not being displayed.)

Score calculations

The leisure activity items are translated to the midpoints of the frequency range (i.e., 0, 1.5, 3.5, or 6, respectively, for days of the week). The hours per day are translated to the midpoints of the hours range (i.e., .5, 1.5, 3, or 5, respectively). Hours per day is then calculated for each leisure activity item (freq*hrs/7).

If the less than 1 hour worked item (WORK1HR) is answered less than 1 hour, this item is calculated as 1 hour worked for the total score.

An individual response of:

.D = Don't know
.R = Refused

for any leisure activity frequency item or household activity item is treated as missing data and the total score is set to missing.

If the occupational activity level item or the leisure activities hours per day items are missing, they are replaced by the median for that item. The median of the item is obtained using all available data for that visit. If the obtained median is a decimal number, it is rounded down. If there are more than 3 occupational activity level/ hours per day items missing, then the total score is set to missing.

(Note: Pages 35Q-39Q of the Follow-up Visit Workbook are not being displayed.)